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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 495/04, A61K 31/4365, A61P 3/10 | A1

(11) International Publication Number: **WO 00/14090**

(43) International Publication Date: 16 March 2000 (16.03.00)

(21) International Application Number: PCT/DK99/00448

(22) International Filing Date: 23 August 1999 (23.08.99)

(30) Priority Data:
PA 1998 01108 2 September 1998 (02.09.98) DK

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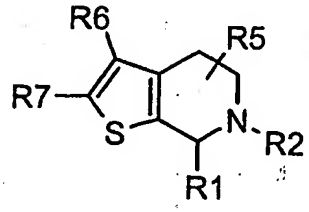
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: 4,5,6,7–TETRAHYDRO–THIENO[2,3–C]PYRIDINE DERIVATIVES



(I)

(57) Abstract

A compound of general formula (I) wherein R1 is C_{1-8}–alkyl, C_{2-8}–alkenyl, C_{3-8}–cycloalkyl, C_{5-8}–cycloalkenyl, Q or aryl; R2 is C_{1-8}–alkyl, C_{2-8}–alkenyl, C_{3-8}–cycloalkyl, C_{5-8}–cycloalkenyl, aralkyl or COR3; R3 is C_{1-8}–alkyl, C_{2-8}–alkenyl, C_{3-8}–cycloalkyl, C_{5-8}–cycloalkenyl, w or aryl; R5, R6, R7 being independently selected from amino–C_{1-6}–alkyl, hydroxy–C_{1-6}–alkyl, hydrogen, C_{1-6}–alkyl, aryl, aralkyl, aryloxy, aryloxy–C_{1-6}–alkyl, benzyl, halogen, hydroxy, mercapto, cyano, nitro, carboxy, carbamoyl, $CONHC_{1-4}$–alkyl, $CON(C_{1-4}$ alkyl$)_2$, C_{1-4}–acyl, C_{1-4}–alkoxy, C_{1-4}–alkylthio, $-SOC_{1-6}$–alkyl, $-SO_2C_{1-6}$–alkyl, C_{1-4}–alkoxycarbonyl, C_{1-4}–alkanoyloxy, amino, optionally substituted mono– or di–C_{1-6}–alkylamino, acylamino, $-NC_{1-4}$–alkylCOC_{1-4}–alkyl, –SO3H, $-SO2NH-C_{1-6}$–alkyl, tetrazolyl, perhalomethyl, perhalomethoxy R1, R2 and R3 are all optionally substituted with one or more substituents; or salt thereof with a pharmaceutically acceptably acid or base, or any optical isomer, pharmaceutical composition containing them, and the use of such compound for preparing medicaments for the treatment of diseases of the endocrinological system, preferably hyperglycaemia or diabetes.

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4,5,6,7-Tetrahydro-thieno[2,3-c]pyridine Derivatives,

Field of the invention

The present invention relates to 4,5,6,7-tetrahydro-thieno[2,3-c]pyridine derivatives, to compositions comprising the compounds, to the use of these compounds as medicaments and their use in therapy, e.g. to their use for treatment of human and animal disorders. The invention relates to modulation of the activity of molecules with glucose-6-phosphate recognition units, including glucose-6-phosphatases (G-6-Pases) in *in vitro* systems, microorganisms, eukaryotic cells, whole animals and human beings, especially in the treatment of diseases related to glucose metabolic pathways.

Background of the invention

Glucose is the major energy substrate in mammals and regulation of blood glucose levels within a narrow range seems to be of crucial importance to devoid serious physiological complications as seen in diabetes (DeFronzo, Bonadonna, & Ferrannini. 1992). Blood glucose homeostasis is maintained by dietary intake of carbohydrates, the uptake of glucose by peripheral tissues and the brain, and storage or release of glucose from the liver. The liver therefore seems to play a major role in the homeostatic regulation of blood glucose levels. Gluconeogenesis and glycogenolysis are the two metabolic pathways from which glucose can be produced in the liver. These pathways are under tight hormonal control. Insulin resistance and insulin deficiency have a substantial impact on glucose production in the liver (Consoli. 1992; DeFronzo, Bonadonna, & Ferrannini. 1992; Clore, Stillman, Stevens, Blackard, Levy, & Richmond. 1996). Glucose-6-phosphatase (G-6-Pase) catalyses the terminal step in the above mentioned pathways by converting glucose-6-phosphate (G-6-P) to glucose, and is largely situated in the liver, with some expression in the kidney after prolonged fasting. The G-6-Pase is a multicomponent system comprising of the G-6-Pase catalytic enzyme with its active site located at the luminal site of the endoplasmic reticulum (microsomal fraction), a specific transporter T1 which mediates entry of G-6-P into the luminal compartment, and transporter T2 and T3 which mediates export to the cytosol of inorganic phosphate and glucose, respectively (Nordlie, Bode, & Foster. 1993; Sukalski & Nordlie. 1989). It has been shown that the rate of hydrolysis of G-6-P and the hepatic glucose output were increased under diabetic conditions (Lyall, Grant, Scott, & Burchell. 1992; DeFronzo, Bonadonna, & Ferrannini. 1992). The increased activity could mainly be

accounted for by increased G-6-Pase catalytic enzyme protein (Argaud, Zhang, Pan, Maitra, Pilkis, & Lange. 1996; Burchell & Cain. 1985). This makes G-6-Pase enzyme a potential target in control of excess glucose production seen in diabetes.

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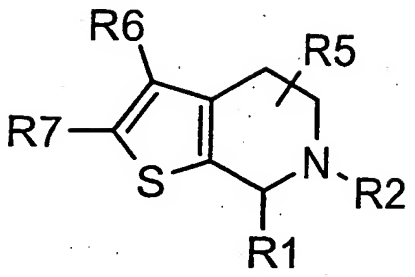
Description of the invention

The present invention relates to compounds of the general formula (I):



Formula (I)

wherein

R1 is a saturated straight or branched C_{1-8}-hydrocarbon chain optionally substituted with one or more substituents,

an unsaturated straight or branched C_{2-8}-hydrocarbon chain optionally substituted with one or more substituents,

a saturated C_{3-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,

an unsaturated C_{5-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,

Q optionally substituted with one or more substituents or

aryl optionally substituted with one or more substituents.

R2 is a saturated straight or branched C_{1-8}-hydrocarbon chain optionally substituted with one or more substituents,

an unsaturated straight or branched C_{2-8}-hydrocarbon chain optionally substituted with one or more substituents,

a saturated C_{3-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,

an unsaturated C_{5-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,

aralkyl optionally substituted with one or more substituents or

COR3 optionally substituted with one or more substituents,

R3 is a saturated straight or branched C_{1-8}-hydrocarbon chain optionally substituted with one or more substituents,

an unsaturated straight or branched C_{2-8}-hydrocarbon chain optionally substituted with one or more substituents,

a saturated C_{3-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,

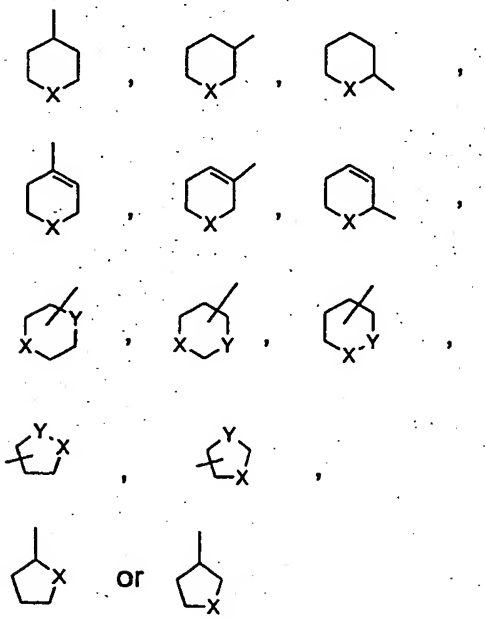
an unsaturated C_{5-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,

an aryl optionally substituted with one or more substituents,

an aralkyl optionally substituted with one or more substituents or

W optionally substituted with one or more substituents.

Q and W are independently selected from the list consisting of



X and Y are independently selected from the group consisting of NR4, O, S, >SO, $>SO_2$,

and **R4** is selected from the list consisting of hydrogen,

a saturated straight or branched C_{1-8}-hydrocarbon chain optionally substituted with one or more substituents,

an unsaturated straight or branched C_{2-8}-hydrocarbon chain optionally substituted

optionally substituted with one or more substituents,

a saturated C_{3-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,

an unsaturated C_{5-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,

C_{1-8}-acyl, C_{1-8}-alkoxycarbonyl, or mono- or dialkylcarbamoyl,

R5, R6, R7 being independently selected from amino-C_{1-6}-alkyl, hydroxy-C_{1-6}-alkyl, hydrogen, C_{1-6}-alkyl, aryl, aralkyl, aryloxy, aryloxy-C_{1-6}-alkyl, benzyl, halogen, hydroxy, mercapto, cyano, nitro, carboxy, carbamoyl, $CONHC_{1-4}$-alkyl, $CON(C_{1-4}alkyl)_2$, C_{1-4}-acyl, C_{1-4}-alkoxy , C_{1-4}-alkylthio, -SOC_{1-6}-alkyl, -SO_2C_{1-6}-alkyl, C_{1-4}-alkoxycarbonyl, C_{1-4}-alkanoyloxy, amino, optionally substituted mono- or di-C_{1-6}-alkylamino, acylamino, -NC_{1-4}-alkylCOC_{1-4}-alkyl, -SO3H, -SO2NH-C_{1-6}-alkyl, tetrazolyl, perhalomethyl , perhalomethoxy

each of the above substituents being selected from the group consisting of halogen, hydroxyl, carboxy, carboxyalkenyl, 2-carboxyethenyl, cyano, nitro, carbamoyl, C_{1-8}-alkylcarbamoyl (preferably metanoyl), C_{1-8}-acyl (preferably acetyl, propionyl, isopropionyl), acetamido, C_{1-8}-alkoxy (preferably methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert.butoxy), C_{1-8}-alkyl, C_{1-8}-alkoxycarbonyl (preferably methoxycarbonyl, ethoxycarbonyl, and propoxycarbonyl), C_{1-8}-alkanoyloxy (preferably acetyloxy, propionyloxy, isopropionyloxy), C_{1-4}-alkylthio (preferably methylthio, ethylthio, propylthio, and isopropylthio), C_{1-4}-alkylsulphinyl (preferably methylsulphinyl and ethylsulphinyl), C_{1-4}-alkylsulphonyl (preferably methylsulphonyl and ethylsulphonyl), C_{1-8}-alkylamino (preferably methylamino, ethylamino), C_{1-8}-dialkylamino (preferably dimethylamino, diethylamino) C_{2-6}-cycloamines (preferably 1-piperidinyl, 1-azeridinyl, 1-pyrrolidinyl, 4-morpholinyl, 1-piperazinyl, 1-azetidinyl), aminoalkyl (preferably one having an amino containing group connected to a C_{1-8}-alkyl group as defined above, such as 2-dimethylaminoethyl and 1-pyrrolidinylmethyl), aminoalkoxy (preferably one having an amino containing group connected via a C_{1-8}-alkyl group as defined above to an oxygen atom, such as 2-dimethylaminoethoxy, 2-(4-morpholinyl)ethoxy and 1-pyrrolidinylmethoxy), aryl (preferably phenyl, furanyl and 4-pyridinyl), aryloxy (preferably phenyloxy), and aralkyloxy (e.g. benzyloxy), hydroxyalkyl, perhaloalkoxy (preferably trifluroromethoxy), alkoxyaryl, C_{1-8}-acyl, perhaloalkyl (preferably trifluoromethyl), oxo, C_{1-4}-

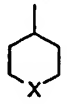
alkanoylamino-C_{1-4}-alkyl, alkoxyoxoindanyl, dimethylhydrazidyl, methylendioxy, thioxothiazolyl, imidazolyl or 2-morpholin-4-ylethoxy.

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form.

In a preferred embodiment the invention relates to compounds of general formula (I) wherein R5, R6 and R7 is hydrogen.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R2 is COR3 wherein R3 is as defined above.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R1 is Q optionally substituted with one or more substituents and Q is



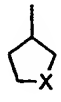
wherein X is as defined above.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein X is NR4 or O ,preferably NR4, wherein R4 is as defined above.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R4 is a saturated straight or branched C_{1-8}-hydrocarbon chain optionally substituted with one or more substituents.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R4 is methyl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R1 is Q optionally substituted with one or more substituent and Q is



wherein X is as defined above.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein X is O.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R1 is N-methylpiperidinyl, tetrahydrofuryl or tetrahydropyranyl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R1 is tetrahydropyran-4-yl, tetrahydrofuran-3- yl or 1-methylpiperidin-4-yl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R1 is optionally substituted phenyl, thienyl preferably 2-thienyl, 3-thienyl, 4-thienyl 5-thienyl or furanyl, preferably 2-furanyl, 3-furanyl, 4-furanyl, 5-furanyl, Benzo[1,3]dioxol preferably Benzo[1,3]dioxol-5yl, pyridyl or cyclohexyl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein the substituents of R1 are selected from the group consisting of halogen, perhaloalkyl, perhaloalkoxy, C_{1-6}-alkoxy, C_{1-8}-alkyl ,C_{1-8}-alkylamino, C_{1-8} -dialkylamino or C_{2-5} -cycloalkylamino.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein the substituents of R1 are selected from the group consisting of chloro, fluoro trifluoromethyl, trifluoromethoxy, methoxy, methyl or dimethylamino.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R1 is selected from the group consisting of phenyl, 4-chlorophenyl, 3-fluorophenyl, 2,4-chlorophenyl, 3,5-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 4-dimethylaminophenyl, 4-pyridyl, 2-thienyl, 5-chloro-2-thienyl, 3-chloro-2-thienyl, Benzo[1,3]dioxol-5yl, cyclohexyl or 4-methoxycyclohexyl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R3 is a saturated straight or branched C_{1-8}-hydrocarbon chain optionally substituted with one or more substituents.

In another preferred embodiment the invention relates to compounds of general formula (I). wherein R3 is a saturated straight or branched C_{1-4}-alkyl optionally substituted with one or more substituents.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R3 is an unsaturated straight or branched C_{2-6}-hydrocarbon chain optionally substituted with one or more substituents.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R3 is an unsaturated straight or branched C_{2-4}-alkenyl optionally substituted with one or more substituents.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R3 is a saturated C_{3-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents.

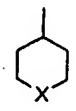
In another preferred embodiment the invention relates to compounds of general formula (I), wherein R3 is a saturated cyclohexyl optionally substituted with one or more substituents.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R3 is an aryl optionally substituted with one or more substituents.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R3 is phenyl, alkoxyphenyl, dialkoxyphenyl, hydroxyphenyl, indanyl, imidazolyl, pyridyl, benzofuranyl, indolyl, benzimidazolyl, thienyl, furanyl, pyranyl optionally substituted with one or more substituents.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R3 is W optionally substituted with one or more substituents wherein W is as defined above.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein W is optionally substituted with one or more substituents and W is



wherein X is as defined above.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein X is NR4 and R4 is as defined above.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R4 is a saturated straight or branched C_{1-8}-hydrocarbon chain optionally substituted with one or more substituents or R4 is a C_{1-8}-acyl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R4 is methyl or methanoyl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein the substituents being selected from the group consisting halogen, hydroxyl, C_{1-4}-alkoxy, C_{1-4}-alkyl, C_{1-4}-alkylthio, C_{1-4}-alkylsulphinyl, aryl, aryloxy, hydroxyalkyl, perhalomethoxy, C_{1-8}-acyl, perhalomethyl, oxo, C_{1-4}-alkanoylamino-C_{1-4}-alkyl, alkoxyoxoindanyl, dimethylhydrazidyl, methylendioxy, thioxothiazolyl, imidazol, aminoalkoxy, carboxy, carboxyalkenyl, cyano or C_{1-8}-alkanoyloxy.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein the substituents being selected from the group consisting fluorine, chlorine, bromine, hydroxyl, methoxy, ethoxy, methyl, methylthio, methylsulphinyl, furanyl, thienyl, phenyl, indolyl, pyranyl, dimethoxyphenyl, methoxyphenyl, hydroxyphenyl, hydroxymethyl, trifluoromethoxy, trifluoromethyl, imidazol, methanoyl, oxo, methanoylamino-methyl, methoxyoxoindanyl, dimethylhydrazidyl, methylendioxy, thioxothiazolyl, carboxy, cyano, acetamido, nitro, acetyl, acetyloxy, dimethylamino, 2-dimethylaminoethoxy, 2-carboxyethenyl or 2-morpholin-4-ylethoxy .

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R2 is COR3 wherein R3 is selected from the group consisting of phenyl, 3-methoxyphenyl, 4-methoxyphenyl 4-chlorophenyl, 4-trifluoromethylphenyl, 4-methylphenyl, 3,4-dimethoxyphenyl, 4-ethoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, 4-dimethylaminophenyl, 4-bromophenyl, 4-hydroxyphenyl, 4-hydroxymethylphenyl, 4-nitrophenyl, 4-cyanophenyl, 4-methylthiophenyl, 4-methylsulfonylphenyl, 4-acetylphenyl, 4-acetamidophenyl, 4-acetoxyphenyl, 3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3-chloro-4-methoxyphenyl, indolyl, 1H-indol-5-yl, and 1H-benzimidazol-5-yl, 2-(4-methoxyphenyl)-ethenyl, 2-(3-methoxyphenyl)-ethenyl, 2-(4-chlorophenyl)-ethenyl, 2-(4-fluorophenyl)-ethenyl, 2-(4-trifluoromethylphenyl)-ethenyl, 2-(4-methoxyphenyl)-ethyl, 2-(4-chlorophenyl)-ethyl, 4-chlorobenzyl, 4-methoxybenzyl, 2-(2-furyl)-ethenyl, 2-(4,5-dimethyl-2-furyl)-ethenyl, 2-(5-methyl-2-furyl)-ethenyl, 2-(3-furyl)-ethenyl, 2-(2-thienyl)-ethenyl, 2-(3-thienyl)-ethenyl, or 4-methoxyphenyl-2-ethenyl, 4-pyridyl, 5-hydroxypyrazin-2-yl, 5-chloro-6-hydroxypyridin-3-yl, 2-chloropyridin-3-yl, benzofuran-2-yl, benzothiophen-2-yl-, 7-methoxybenzofuran-2-yl, furyl, thienyl, chlorothienyl, 5-chlorothiophen-2-yl, or benzimidazol, 1H-benzimidazol-5-yl, 4-methoxycyclohexyl, 4-oxycyclohexyl, N-methylpiperidinyl, tetrahydrofuryl, tetrahydropyranyl, 4-(2-carboxyethenyl)phenyl, 4-(2-dimethylaminoethoxy)-phenyl or 4-(2-morpholin-4-ylethoxy)phenyl.

The present invention relates furthermore to a salt of a compound of the general formula (I) with a pharmaceutically acceptable acid or base.

The compounds according to the invention may optionally exist as pharmaceutically acceptable salts including pharmaceutically acceptable acid addition salts, such as hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, acetic, trifluoroacetic, trichloroacetic, oxalic, maleic, pyruvic, malonic, succinic, citric, tartaric, fumaric, mandelic, benzoic, cinnamic, methanesulfonic, ethanesulfonic, picric and the like, and include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) and incorporated herein by reference; pharmaceutically acceptable metal salts, such as lithium, sodium, potassium, or magnesium salts and the like; or - optionally alkylated - ammonium salts; or amine salts of the compounds of this invention, such as the sodium, potassium, C_{1-8}-alkylamine, di (C_{1-8}-alkyl) amine, tri (C_{1-8}-alkyl) amine and the corresponding omega-hydroxy analogues (e.g. methylamine, ethylamine, propylamine, dimethylamine, diethylamine,

dipropylamine, trimethylamine, triethylamine, tripropylamine, di(hydroxyethyl)amine, and the like; Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present compounds are able to form. The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent. The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

Examples of the saturated aliphatic hydrocarbon chains having 1 to 8 carbon atoms include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.butyl, tert.butyl, n-pentyl, isopentyl, neopentyl, tert.pentyl, n-hexyl, isohexyl, octyl. Example of the unsaturated aliphatic hydrocarbon chains having 2 to 8 carbon atoms include ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, ethynyl, 1-propionyl, 2-propionyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl. Examples of the saturated alicyclic hydrocarbon group having 3 to 8 carbon atoms include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. Examples of unsaturated C_{5-8}-alicyclic hydrocarbon group having 5 to 8 carbon atoms such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cyclooctenyl.

The term "aryl" as used herein refers to an aryl or a heteroaryl and includes phenyl, alkoxyphenyl, dialkoxyphenyl, hydroxyphenyl, biphenyl, indene, indane, fluorene, naphthyl (1-naphthyl, 2-naphthyl), anthracene (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), pyrrolyl (2-pyrrolyl), pyrazolyl (e.g. 3-pyrazolyl, 4-pyrazolyl and 5-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3- pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-

benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzo[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl), benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]thiophenyl (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]thiophenyl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benzoxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl), furanyl (e.g. 2-furanyl, 3-furanyl, 4-furanyl and 5-furanyl), thienyl (e.g. 2-thienyl, 3-thienyl, 4-thienyl and 5-thienyl), tetrazolyl (5-tetrazolyl), isoxazolyl (3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), isothiazolyl (3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), 1,2,3-oxadiazolyl (1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl), 1,2,3-thiadiazolyl (1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl), 1,2,4-oxadiazolyl (1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl), 1,2,4-thiadiazolyl (1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl),1,3,4-oxadiazolyl (1,3,4-oxadiazol-2-yl, 1,3,4-oxadiazol-5-yl), 1,3,4-thiadiazolyl (1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl), 1,2,5-oxadiazolyl (1,2,5-oxadiazol-3-yl, 1,2,5-oxadiazol-5-yl),1,2,5-thiadiazolyl (1,2,5-thiadiazol-3-yl, 1,2,5-thiadiazol-5-yl), benzo[d]isoxazolyl (benzo[d]isoxazol-3-yl, benzo[d]isoxazol-4-yl, benzo[d]isoxazol-5-yl, benzo[d]isoxazol-6-yl, benzo[d]isoxazol-7-yl), benzo[d]isothiazolyl (benzo[d]isothiazol-3-yl, benzo[d]isothiazol-4-yl, benzo[d]isothiazol-5-yl, benzo[d]isothiazol-6-yl, benzo[d]isothiazol-7-yl), benzo [1,3]dioxol (benzo[1,3]dioxol-5-yl), pyranyl, N-methylpiperidinyl, tetrahydrofuryl, or tetrahydropyranyl

The term "halogen" as used herein means fluorine, chlorine, bromine or iodine.

The term "perhalomethyl" as used herein means trifluoromethyl, trichloromethyl, tribromomethyl or triiodomethyl.

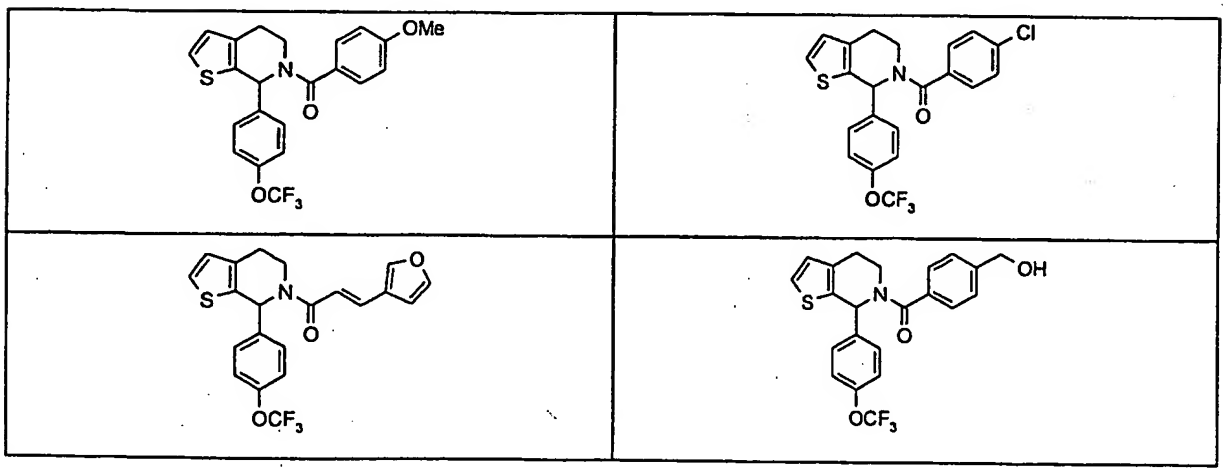
The term "perhalomethoxy" as used herein means trifluoromethoxy, trichloromethoxy, tribromomethoxy or triiodomethoxy.

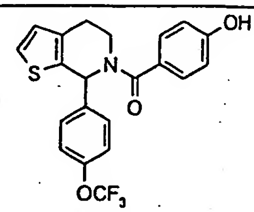
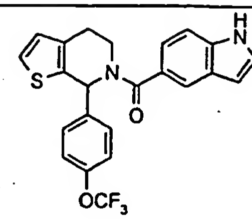
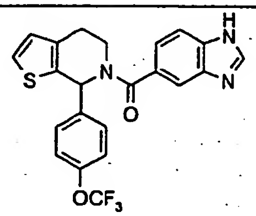
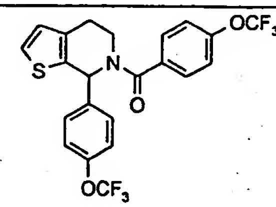
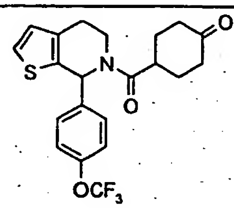
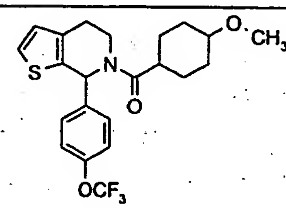
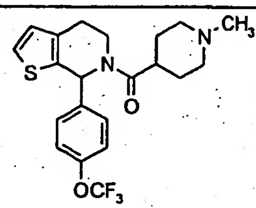
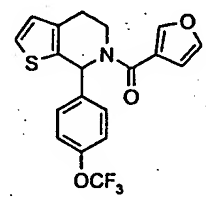
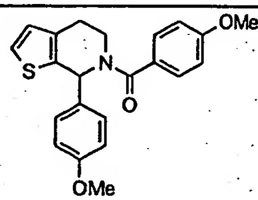
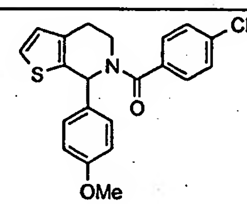
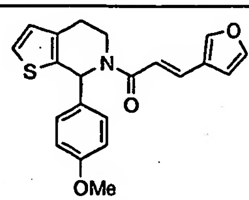
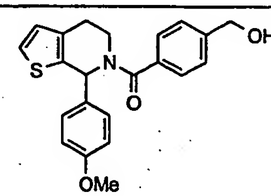
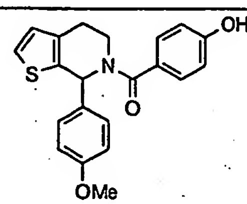
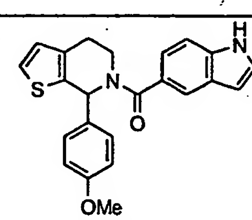
The term C_{1-8}-alkyl as used herein, refers to a straight, branched or cyclic C_{1-8}-hydrocarbon chain.

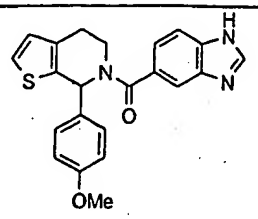
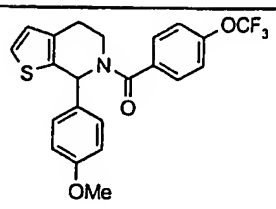
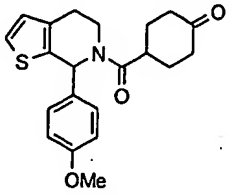
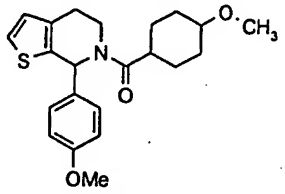
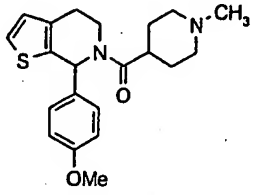
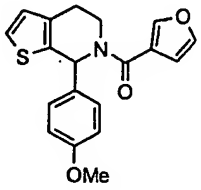
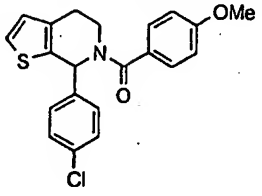
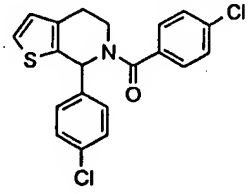
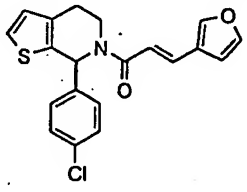
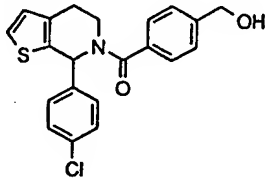
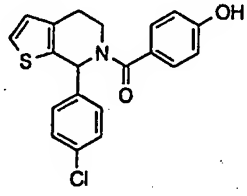
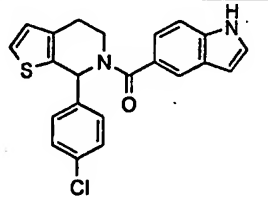
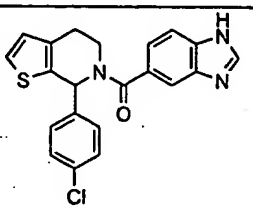
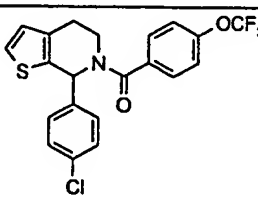
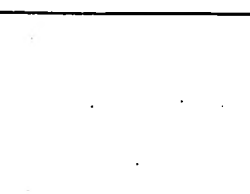
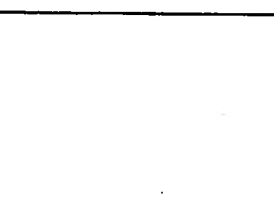
The term "aralkyl" as used herein refers to an optionally substituted aryl residue as defined above, connected to an optionally substituted C_{1-8}-alkyl as defined above. Examples of the aralkyl residue include benzyl, 2-phenylethyl, 2-phenylethenyl, 3-(2-pyridyl)propyl, 3-phenylpropyl, 1-naphtylmethyl, 2-(1-naphtyl)ethyl and the like.

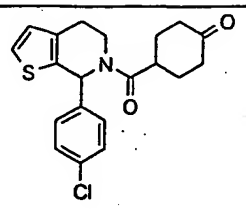
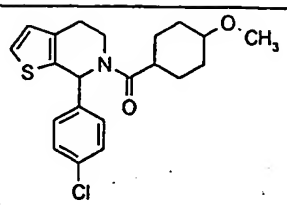
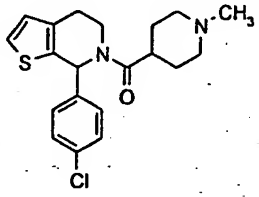
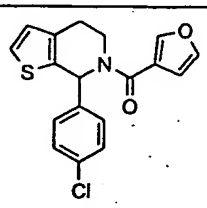
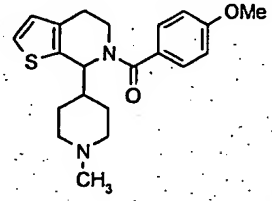
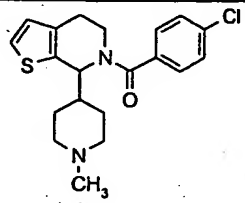
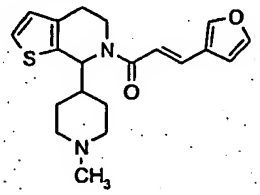
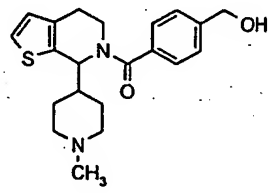
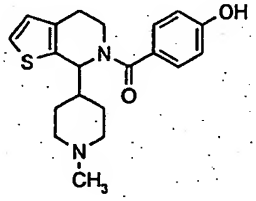
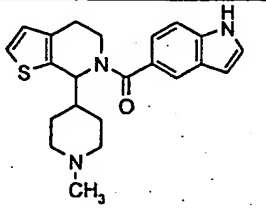
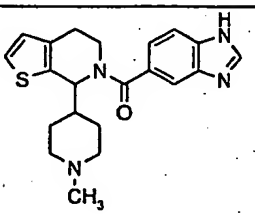
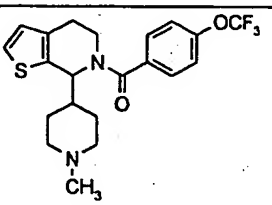
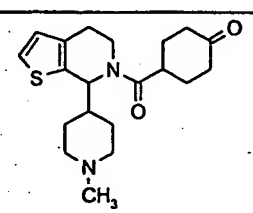
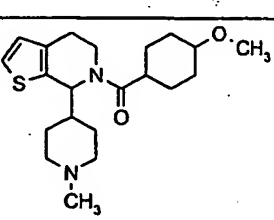
The term "C_{1-8}-alkoxy" as used herein, alone or in combination, refers to a straight or branched monovalent substituent comprising a C_{1-8}-alkyl group as defined above linked through an ether oxygen having its free valence bond from the ether oxygen and having 1 to 8 carbon atoms e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentoxy.

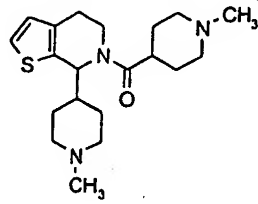
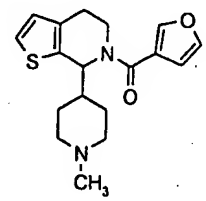
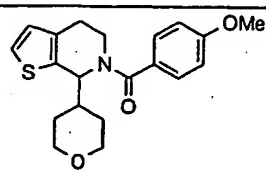
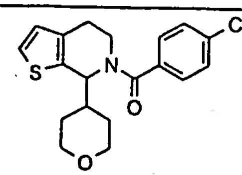
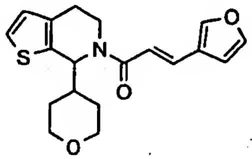
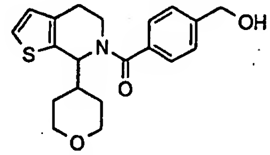
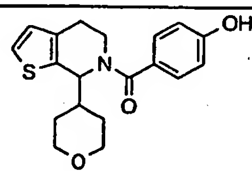
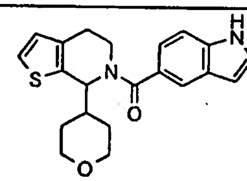
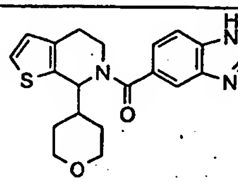
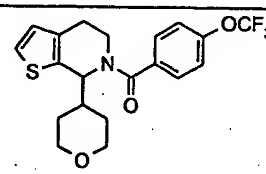
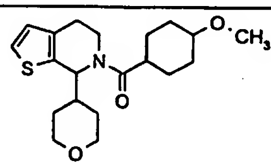
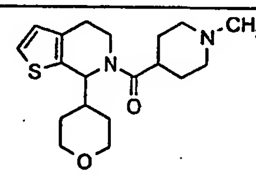
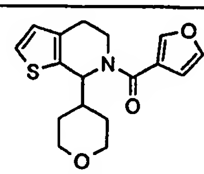
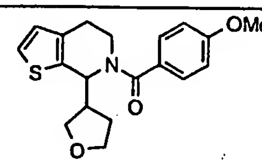
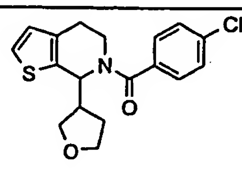
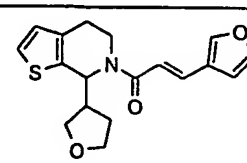
Preferred compounds of the invention are:

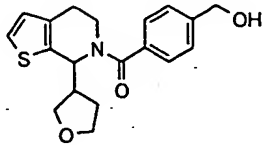
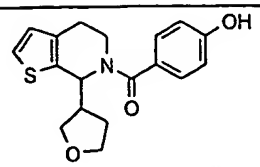
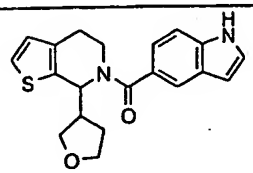
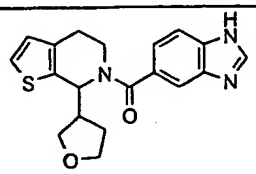
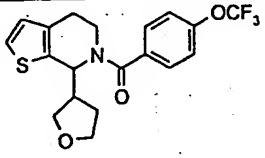
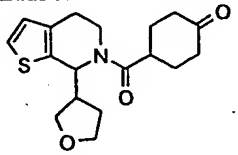
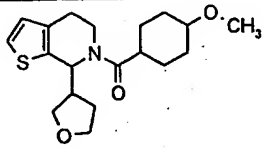
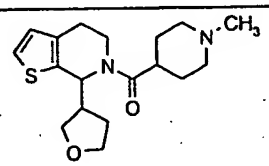
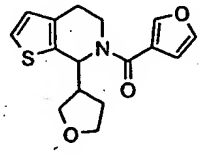
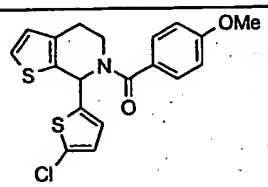
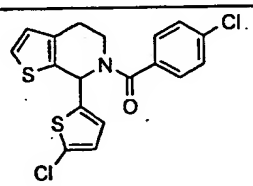
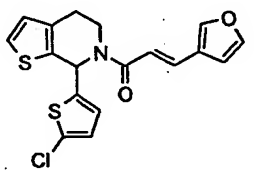
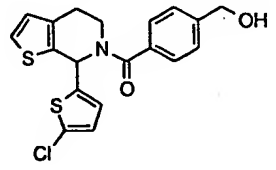
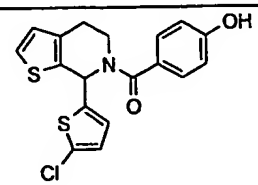


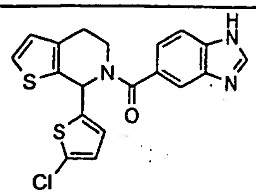
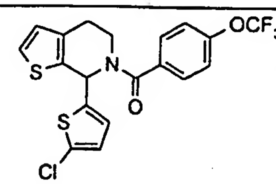
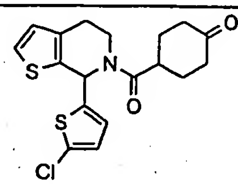
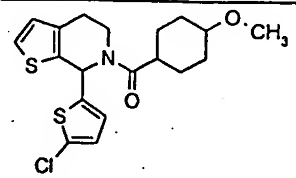
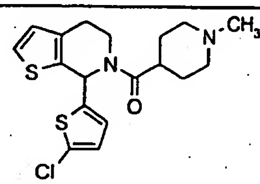
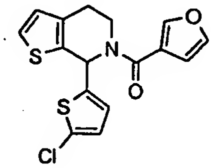
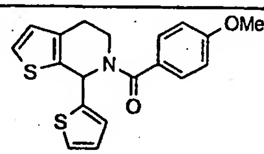
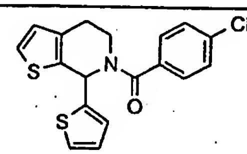
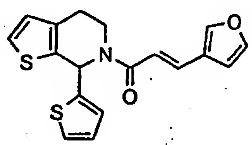
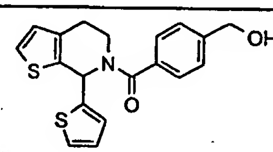
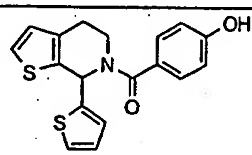
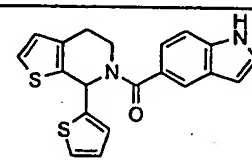
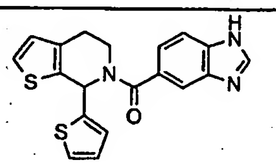
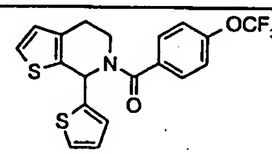
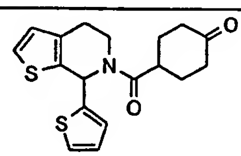
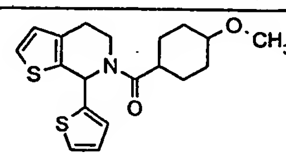
	
	
	
	
	
	
	

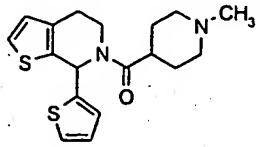
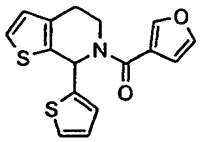
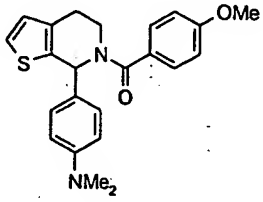
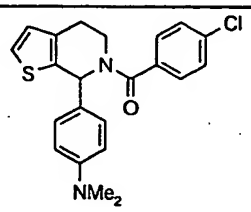
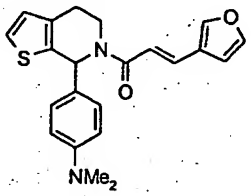
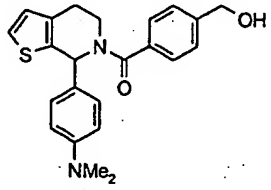
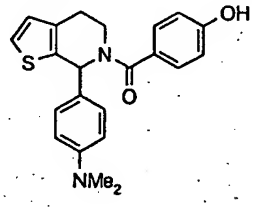
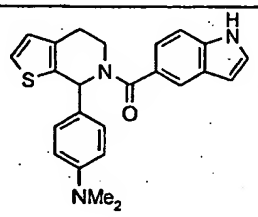
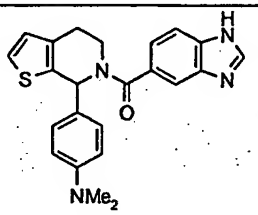
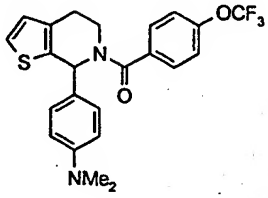
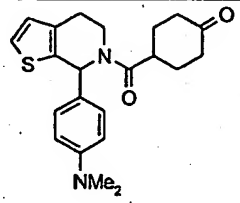
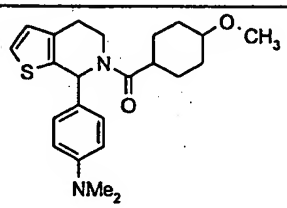
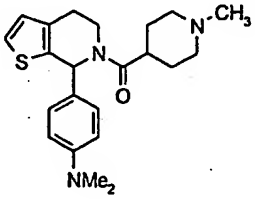
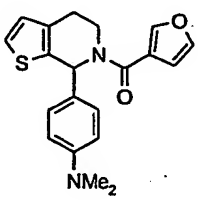
	
	
	
	
	
	
	
	

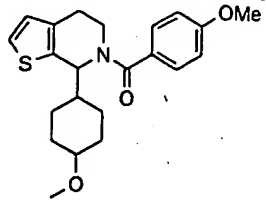
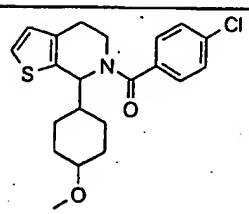
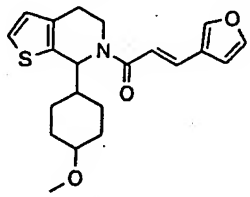
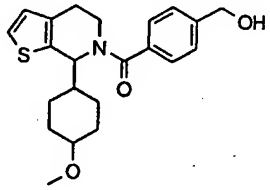
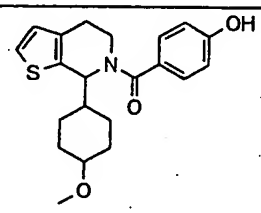
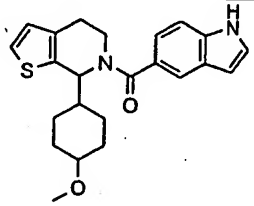
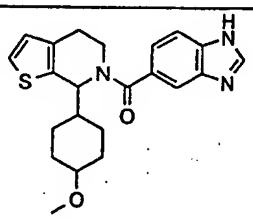
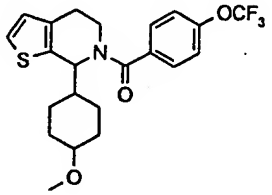
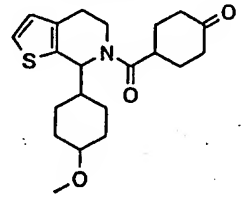
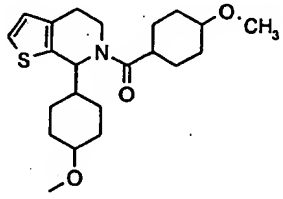
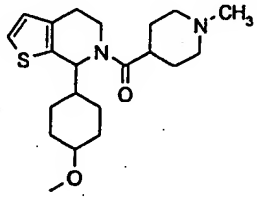
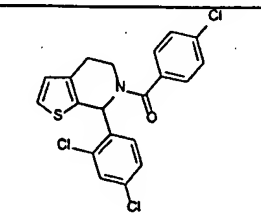
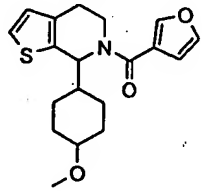
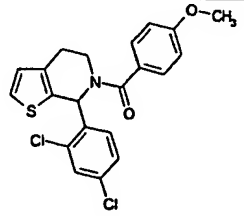
	
	
	
	
	
	
	

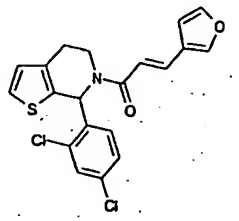
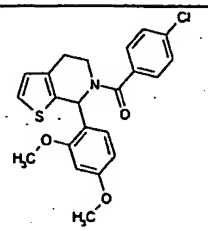
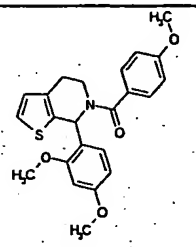
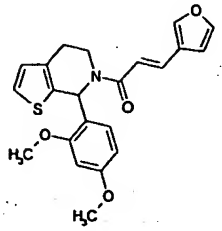
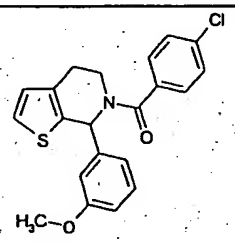
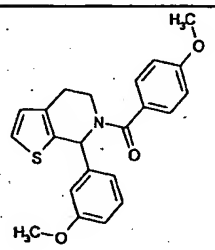
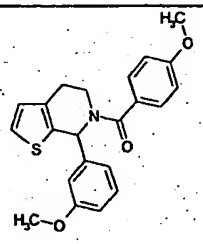
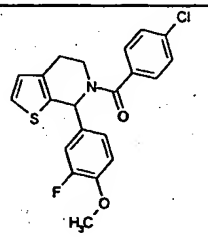
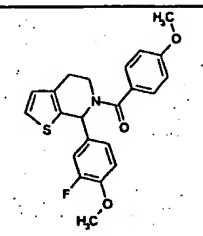
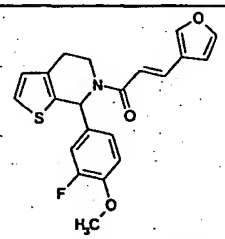
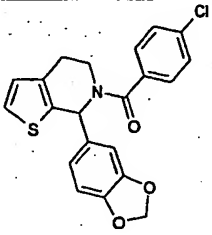
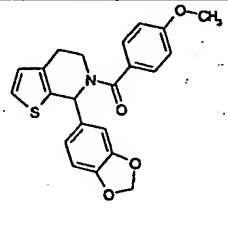
 CH3 N S N O N CH3	 O S N O N CH3
 OMe S N O O	 Cl S N O O
 O S N O O	 OH S N O O
 OH S N O O	 H N S N O O
 H N N S N O O	 OCF3 S N O O
 O CH3 S N O O	 N CH3 S N O O
 O S N O O	 OMe S N O O
 Cl S N O O	 O S N O O

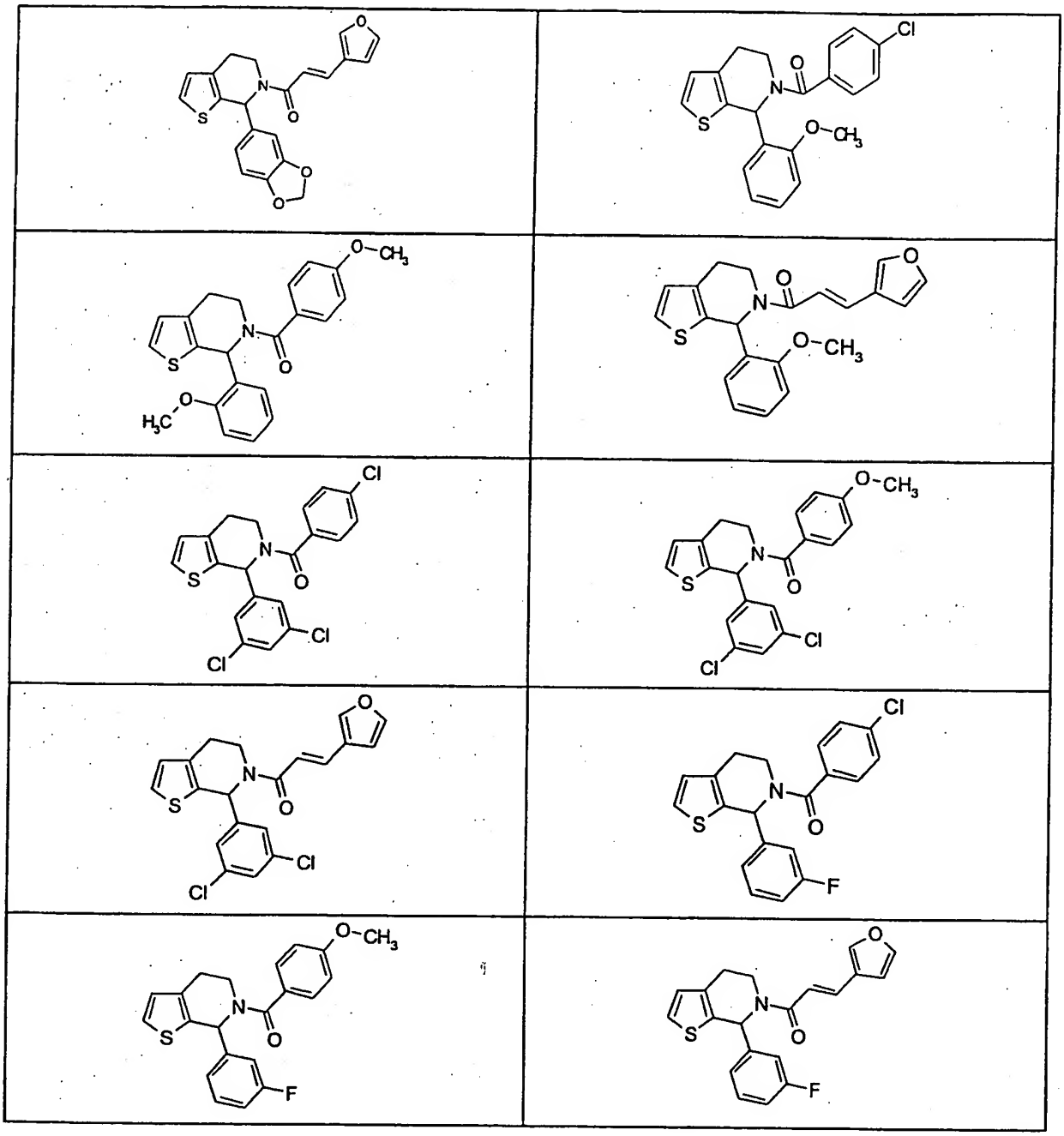
	
	
	
	
	
	
	
	



and salts there of with a pharmaceutically acceptable acid or base.

The compounds of the present invention are normoglycaemic agents (i.e. compounds that are able to normalise blood glucose levels from hyper-/hypoglycemic conditions) that interact with the glucose-6-phosphatase catalytic enzyme activity, and hence make them useful in the treatment and prevention of various diseases of the endocrinological system, especially

ailments related to carbohydrate metabolism and especially the glucose metabolism, e.g. hyperglycaemia, diabetes mellitus, and especially non-insulin dependent diabetes mellitus (NIDDM) including long-term complications, such as retinopathy, neuropathy, nephropathy, and micro- and macroangiopathy, and hypoglycaemia resulting from, e.g., glycogen storage disease (von Gierke's Disease all types). Moreover, the present compounds are useful in the prophylactic treatment of hyperlipidaemia, hypertension, liver and bile diseases, and atherosclerosis associated with diabetes. The present compounds are especially useful in the treatment of diseases associated with an increased or reduced activity of the glucose-6-phosphatase complex, e. g. the G-6-Pase catalytic enzyme.

Accordingly, in another aspect the invention relates to a compound of the general formula (I) or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use. Preferably for treatment or prevention of diseases of the endocrinological system, preferably hyperglycaemia or diabetes.

Furthermore, the invention also relates to the use of a compound of the general formula (I) or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament.

Furthermore, the invention also relates to the use of a compound of the general formula (I) or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament for the treatment or prevention of diseases of the endocrinological system, preferably hyperglycaemia or diabetes.

Furthermore, the invention also relates to the use of a compound of the general formula (I) or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament for the treatment or prevention of glycogen storage disease or hypoglycaemia.

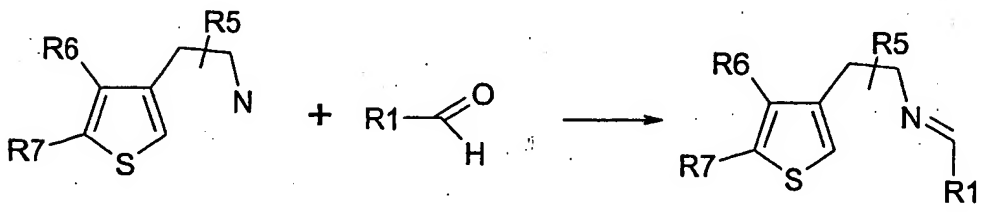
The invention relates furthermore to a method of treating or preventing diseases of the endocrinological system, preferably hyperglycaemia or diabetes in a subject in need thereof comprising administering an effective amount of a compound of the general formula (I) to said subject.

Methods

The compounds of the invention can be prepared by the following methods:

a)

Reacting a compound of the general formula II with a compound of the general structure III under formation of a compound of the general structure IV according to the following reaction scheme.



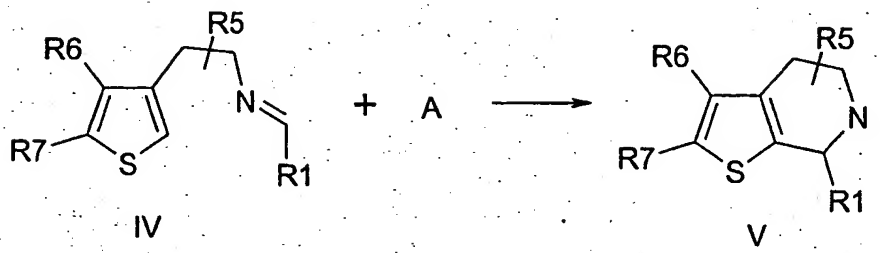
II III IV

The meaning of R1,R5,R6, and R7 is described above.

Compounds of the general formula II can conveniently be prepared from purchasable compounds using methods described in the literature e.g. M. Cardellini et al. Eur. J. Med. Chem. (1994) 29, 423 - 429.

b)

Reacting a compound of the general formula IV with an agent A capable of introducing a ring closure forming a compound of the general structure V according to the reaction scheme below.



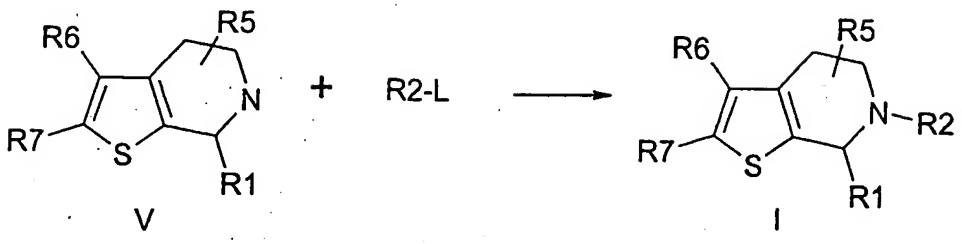
IV V

Agents which can introduce ring closure could be chosen among Trifluoroacetic acid, Phosphoroxy chloride, Phosphorpentoxide, Sulphuric acid, Methanesulphonic acid, mixtures thereof , or other agents known in the art.

R1,R5,R6,and R7 has the meaning described above.

c)

Reacting a compound of the formula V with a compound of the general formula R2-L under formation of a compound of the general formula I



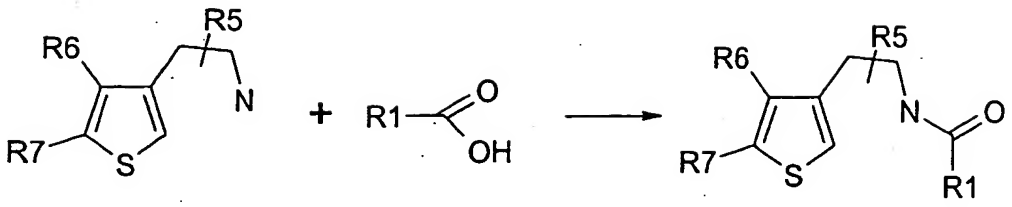
R1,R2,R5,R6, and R7 has the meaning defined above.

L being a good leaving group as halogen, sulfate, sulfonate or acyl ; when R2 is R3CO- where R3 is as defined above, L can be selected from fluorine, chlorine, bromine, iodine, 1-imidazolyl, 1,2,4-triazolyl, 1-benzotriazolyloxy, 1-(4-aza benzotriazolyl)oxy, pentafluorophenoxy, N-succinyloxy 3,4-dihydro-4-oxo-3-(1,2,3-benzotriazinyl)oxy, R3COO- , or any other leaving group known to act as a leaving group in acylation reactions. A base can be either absent (i.e. compound V acts as a base) or triethylamine, N-ethyl-N,N-diisopropylamine, N-methylmorpholine, 2,6-lutidine, 2,2,6,6-tetramethylpiperidine, potassium carbonate, sodium carbonate, caesium carbonate or any other base known to be useful in acylation reactions.R3CO-L can be prepared by activation of the corresponding carboxylic acid in the presence or absence of the alcohol component of the activated ester, such as HOBt, HOAt, HOSu, HOPFP, using various carbodiimide reagents, such as dicyclohexyl- or diisopropylcarbodiimide, EDAC and the like, or using phosphorous based activation reagents, such as PyBOP, PyBrOP, TFFH and the like, carbonyldi-azole reagents such as carbonyldiimidazole, carbonyldi-1,2,4-triazole, or any other activation or coupling reagent known to those skilled in the art.

Compounds of the general formula V can also be prepared by the following reactions.

d)

Reacting a compound of the general formula II with a compound of the general formula VI under formation of a compound of the general formula VII as shown in the reaction scheme below.



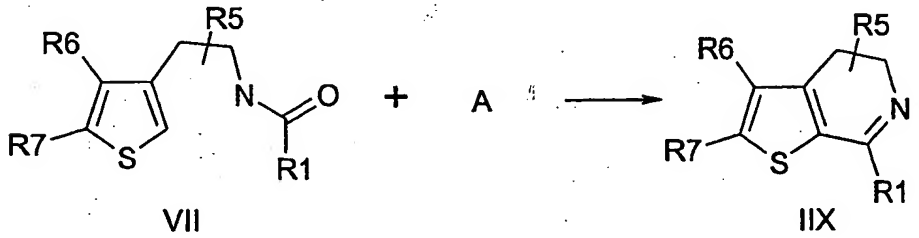
II VI VII

R1,R5,R6,R7 has the meaning defined above.

The reaction can conveniently be carried out by by activation of the carboxylic acid with agents such as such as HOBt, HOAt, HOSu, HOPFP, using various carbodiimide reagents, such as dicyclohexyl- or diisopropylcarbodiimide, EDAC and the like, or using phosphorous based activation reagents, such as PyBOP, PyBrOP, TFFH and the like, carbonyldi-azole reagents such as carbonyldiimidazole, carbonyldi-1, 2,4-triazole, or any other activation or coupling reagent known to those skilled in the art.

e)

Reacting a compound of the formula VII with an agent A capable of introducing ring closure under formation of a compound of the general structure IIX as depicted in the reaction scheme below.

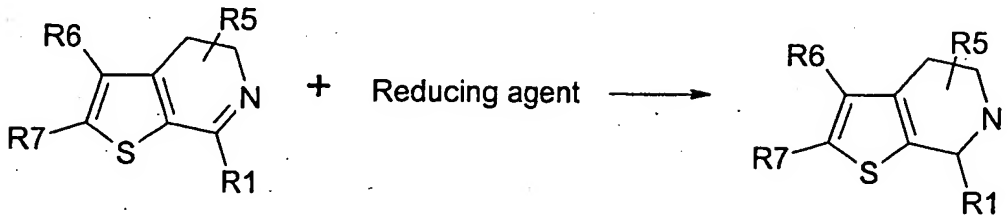


VII IIX

R1,R5,R6,R7 having the meaning defined above, A being an agent which can introduce ring closure like Trifluoroacetic acid, Phosphoroxy chloride, Phosphorpentoxide, Sulphuric acid, Methanesulphonic acid, or other acids , or anhydrides or mixtures thereof or other agents capable of introducing ring closure under water absorption known in the art.

f)

Reacting a compound of the general formula IIX with a reducing agent under formation of a compound of the general structure V.



IIX V

R1,R5,R6,R7 having the meaning defined above.

The reducing agent can be chosen among Sodium Borohydride, Lithium Aluminium Hydride, Lithium triethylborohydride , Aluminium hydride and other reducing agents known in the art.

Or the compounds of formulae (I) or may be prepared by art-recognized procedures from known compounds or readily preparable intermediates.

Examples of the methods which can be used for the synthesis of the starting materials and intermediates for the compounds of the invention can be found in e.g.

S.Gronowitz and E. Sandberg, *Ark. Kemi* ,1970, **32**,217 - 227;

G. Wolf and F.Zymalkowski, *Arch. Pharm. (Weinheim)* 1976, **309**, 279 -288.

E.J.Browne, *Aust. J. Chem.*, 1984, **37**, 367 - 379.

Tupper D.E. et al., *J. Heterocyclic Chem.*, 33, 1123-9 (1996), Stokker G.E., *Tetrahedron Lett.*, 37, 5453-6 (1996), Nakagawa, M. et al., *Chem. Pharm. Bull.*, 41, 287-91 (1993), Singh H. et al., *Heterocycles*, 23, 107-10 (1985), Skinner W.A. et al., *Can. J. Chem.*, 43, 2251-3 (1965). P. Kumar et al., *J. Heterocyclic Chem.*, **19**, 677-9 (1982), L. K. Lukanov et al., *Synthesis*, **1987**, 204-6, A. L. Stanley & S. P. Stanforth, *J. Heterocyclic Chem.*, **31**, 1399-1400 (1994), A. K. Bose et al., *J. Org. Chem.*, **56**, 6968-70 (1991), K. Kementani et al., *Heterocycles*, **3**, 311-41 (1975), E. Domonguez et al., *Tetrahedron*, **43**, 1943-8 (1987), J. B. Bremner et al., *Aust. J. Chem.*, **41**, 1815-26 (1988), M. J. O'Donnel et al., *Tetrahedron. Lett.*, **23**, 4259-62 (1982).

Pharmacological methods

The ability of compounds to inhibit glucose-6-phosphatase (G-6-Pase) catalytic enzyme activity from pig liver microsomes was tested in the following way:

Pig liver microsomes were prepared in a buffer containing 250 mM sucrose, 1 mM EDTA, 25 mM HEPES and 250 mg/l Bacitrazin (pH 7.5) essentially as described by Arion et al.,1980 (Arion, Lange,.& Walls. 1980). Microsomes were kept at -80 °C until use.

Prior to measurement microsomes were treated with Triton X-100 (0.04%) ("disrupted microsomes"). G-6-Pase activity were assayed for 6 min at 30°C in a total volume of 325 µL containing 0.5 mM glucose-6-phosphate, 30 mM MES (pH 6.5), test compound and disrupted microsomes (0.05 mg). The reaction was terminated by addition of 100 µL Sigma phosphorus reagent (cat no 360-3C). This mixture was allowed to stand for 2 min, where the absorbance (A) was measured at 340 nm. All values were corrected for blank. The inhibitory effect was expressed as percent of control value, i.e. IC_{50} is the concentration of a compound that produces 50% inhibition.

The compounds of the invention are preferably characterized by having a glucose-6-phosphatase inhibitory activity corresponding to an IC_{50} value of less than 100 µM, more preferably less than 10 µM, even more preferably less than 1 µM, still more preferably less than 100 nM.

The compounds according to the invention are effective over a wide dosage range. In general satisfactory results are obtained with dosages from about 0.05 to about 1000 or 5000mg, preferably from about 0.1 to about 500 mg, per day. A most preferable dosage is about 5 mg to about 200 mg per day. The exact dosage will depend upon the mode of administration, form in which the compound is administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

The present invention relate furthermore to a pharmaceutical composition comprising, as an active ingredient, a compound of the general formula (I) or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

The dosage unit of the pharmaceutical compositions according to the invention typically contains from 0.05mg to 1000mg, preferably from 0.1mg to 500mg, or, preferably from 5mg to 200mg per day of the active ingredient, which is, preferably, a novel 4,5,6,7-tetrahydro-thieno[2,3-c]pyridine derivative as described herein or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form thereof; or the active ingredient is a previously described 4,5,6,7-tetrahydro-thieno[2,3-c]pyridine derivative or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form thereof.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intrapulmonary, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

Optionally, the pharmaceutical composition of the invention may comprise a compound of formula I combined with one or more compounds exhibiting a different activity, e.g., a plasma lipid lowering compounds, sulphonylurea like compounds, or other oral agents useful in the treatment of diabetes, or other pharmacologically active material.

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of formula (I) or a pharmaceutically acceptable acid addition salt or metal salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated in any galenic dosage form so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art. The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For administration, preferably nasal administration, the preparation may contain a compound of formula (I) dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes. For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil. Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or

potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet, appropriate for use in this method, may be prepared by conventional tabletting techniques and contains:

Core:	
Active compound (as free compound or salt thereof)	5.0 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	**Ad.**
Coating:	
HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

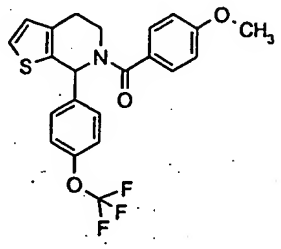
Due to their high degree of activity, the compounds of the invention may be administered to a mammal in need of such treatment, prevention, elimination, alleviation or amelioration of various diseases as mentioned above and especially of diseases of the endocrinological system such as hyperinsulinaemia and diabetes. Such mammals include both domestic animals, e.g. household pets, and non-domestic animals such as wildlife. Preferably the mammal is a human.

EXAMPLES

The processes for preparing compounds of formula (I) and preparations containing them is further illustrated in the following examples which, however, are not to be construed as limiting.

EXAMPLE 1

Preparation of [7-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-6-yl]-(4-methoxyphenyl)methanone



A solution of 2-(3-thienyl)ethylamine (14.7 g, 0.115 mol) and 4-trifluormethoxybenzaldehyde (15.0 g, 0.08 mol) in benzene (200 ml) was refluxed (Dean-Stark trap, H_2O removed) for 4 h. Trifluoroacetic acid (2 ml) was added and the mixture was refluxed for 8 h. After cooling it was made alkaline with NH_4OH and washed with water. The organic phase was dried (K_2CO_3) and evaporated in vacuo to give a residue, which was purified by chromatography on silica gel (200 g). A by-product was removed by elution with benzene, R_F=0.68 (SiO_2; $CHCl_3$/EtOH/NH_4OH = 200:10:1), probably Schiff base (it was decomposed by an attempt to prepare hydrogen oxalate). The crude title base (3.9 g) was obtained by elution with chloroform.

R_F=0.47 (SiO_2; $CHCl_3$/EtOH/NH_4OH=200:10:1).

Hydrogen oxalate : It was prepared by neutralisation of solution of above base in diethyl ether with a solution of oxalic acid dihydrate in acetone. Hydrogen oxalate was contaminated with hydrogen oxalate of 2-(3-thienyl)ethylamine. A suspension of the mixture was repeatedly boiled with water and filtrated. This afforded, after drying, pure 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine, hydrogen oxalate 2.5 g (8 %), m.p. 190-195 °C.

^1H NMR (250 MHz, DMSO-d_6, δ_H) : 9.22 (s, 3 H); 7.59 (d, J=8.6 Hz, 2 H); 7.47 (d, J=4.9 Hz, 1 H); 7.42 (d, J=8.6 Hz, 2 H); 6.97 (d, J=4.9 Hz, 1 H); 5.73 (s, 1 H); 3.35 (bm, 2 H); 2.95 (bm, 2 H).

Calculated for $C_{14}H_{12}F_3NOS$, $C_2H_2O_4$, 1/4 H_2O :

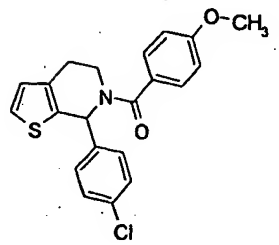
C, 48.79%; H, 3.71%; N, 3.56%; F, 14.47%, S, 8.14%; Found:

C, 48.69%; H, 3.60%; N, 3.42%; F, 14.83%, S, 8.38%.

4-Methoxybenzoic acid (0.1 g, 0.67 mmol) was dissolved in DMF (2 ml) and 1-hydroxybenzotriazole (0.12 g, 0.8 mmol) was added followed by EDAC (0.15 g, 0.8 mmol). The resulting mixture was stirred at room temperature for 30 minutes and then the above 7-(4-trifluormethoxyphenyl)-1,2,3,4-tetrahydrothieno[2,3-c]pyridine as free base (0.24 g, 0.8 mmol) was added and the resulting mixture was stirred at room temperature for 16 hours. Ethyl acetate (15 ml) was added and the mixture was washed with water (3 x 10 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative TLC eluting with a mixture of ethyl acetate and heptane (1:3). This afforded 0.09 g (31%) of the title compound. HPLC-MS: R_t = 16.5 min. m/z: 434 (M+1)

EXAMPLE 2

[7-(4-Chloro-phenyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-6-yl]-(4-methoxy-phenyl)-methanone



2-(3-Thienyl)ethanamine was prepared analogous to the method described by M. Cardellini et al.

Thiophene-3-carboxaldehyde (15.0 g), nitromethane (9.79 g) and sodium methoxide (2 M, 71.25 ml) were mixed in methanol (dry , 50 ml).

The mixture was stirred at room temperature for 2 h, dry diethyl ether (60 ml) was added, the mixture filtered and the isolated crystalline mass dried in vacc.

Subsequently the crystals were added to a mixture of HCl (2 N, 1L) and toluene (1.5L).

The mixture is stirred for 30 min and the organic phase was separated, dried over MgSO4 filtered and evaporated to dryness.

The isolated mass was recrystallised from abs. Ethanol.

Yield of 2-(3-thienyl)-1-nitro ethylene 50 % , m.p. 94.5 C.

2 g of the above mentioned nitro-ethylene was reduced with LiAlH4 (1.71 g) in dry THF (70 ml) reaction time 2.5 h. Work up with NaOH and subsequent extraction with methylene chloride followed by drying of the organic phase with MgSO4 and evaporation giving 75 % of *2-(3-Thienyl)ethanamine* which was used without further purification.

7-(4-Chloro-phenyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine

2-(3-Thienyl)ethanamine (3.15 g) and 4-chlorobenzaldehyde (3.5 g) were mixed without solvent resulting in dissolution af the crystals of the amine followed by precipitation of slightly yellow crystals. The mixture was left at RT for 4h.Trifluoroacetic acid (20 ml) was added and the mixture stirred overnight at RT.

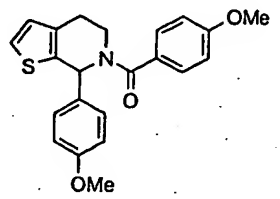
The solvent was evaporated and the resulting mixture extracted between NaOH (4M) and methylene chloride, the organic phase was separated, dried with MgSO4/C and evaporated resulting in an oil which was purified on silicagel using methylene chloride / methanol (9/1) as eluent. Yield of *7-(4-Chloro-phenyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine* 50 %, m.p. 93.6 - 93.8 C.

[7-(4-Chloro-phenyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-6-yl]-(4-methoxy-phenyl)-methanone

7-(4-Chloro-phenyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin (100 mg) in toluene (20 ml) , 4-methoxybenzoyl chloride (68.3 mg) and triethylamine (1 ml) were mixed and the mixture stirred at RT for 2 h. The reaction mixture was extracted once with NaOH (1 M) and once with water, the organic phase dried (MgSO4) and evaporated to dryness resulting in yellow oil which was purified on silicagel using methylene chloride /methanol 19/1 as eluent. The resulting oil was treated with abs ethanol resulting in precipitation of crystals. Yield 91% , m.p. 129.5 - 130.0 C. MS. M+ =383.

EXAMPLE 3

[7-(4-Methoxyphenyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-6-yl]-(4-methoxy-phenyl)-methanone



Was prepared using the same methods as described in example 2 using 2-(3-thienyl)ethanamine (1.21 g) and 4-methoxybenzaldehyde (1.30 g) for the preparation of the imine intermediate (yield 2.4 g) and performing the ring closure with TFA (15 ml), Yield 42 % of *7-(4-methoxyphenyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine* isolated as an oil. MS : M+ = 245.

Method a.

[7-(4Methoxyphenyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-6-yl]-(4-methoxy-phenyl)-methanone

was prepared from 7-(4-methoxyphenyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin (80 mg) in toluene (10 ml) , 4-methoxybenzoyl chloride (66.5 mg) and triethylamine (90 uL) as described in example 2. Yield 80 % of the title compound, MS : M+ = 379.

Method b.

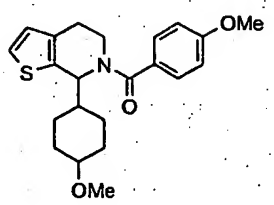
[7-(4Methoxyphenyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-6-yl]-(4-methoxy-phenyl)-methanone

7-(4-methoxyphenyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine (80 mg) in toluene (10 ml) , 4-methoxybenzoic acid (55 mg) ,EDAC (94 mg) and HOBt (44 mg) were mixed in DMF (3 ml). The mixture was stirred overnight , evaporated to dryness and dissolved in ethyl acetate (10 ml).

The organic phase was successively extracted with 10 ml of each of the following: NaOH (1M), water, HCl (0.1 M) , NaOH (1 M) , water. the organic layer dried (MgSO4) and evaporated to dryness giving 100 mg of the title compound (81 %), MS : M+ = 379.

EXAMPLE 4

[7-(4-Methoxycyclohexyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-6-yl]-(4-methoxyphenyl)-methanone



2-(3-Thienyl)ethanamine (3 g) was treated with 4-methoxycyclohexanecarboxylic acid (*cis/trans* mixture , 3.73 g) , HOBT (3.18 g) , and EDAC (6.78 g) in DMF (180 ml). The mixture is stirred overnight , evaporated to dryness.The resulting oil is redissolved in methylene chloride (100 ml) and extracted with NaOH (2 M, 100 ml). The organic phase was separated and further extracted consecutively with sat. Saline (100 ml) , HCl (0.1 M, 100 ml), NaOH (0.5 M, 100 ml) .

The organic layer was isolated, dried over MgSO4, yield 5.75g of 4-methoxycyclohexanecarboxylic acid (2-thiophen-3-yl-ethyl)-amide as an oil (93 %).The 13C NMR spectrum clearly shows the presence of two isomers (*cis* and *trans*).

4-Methoxycyclohexanecarboxylic acid (2-thiophen-3-yl-ethyl)-amide (3.1 g) was dissolved in toluene (50 ml) , POCl3 (3.16 ml) dissolved in toluene (100 ml) was dropwise added, and the mixture was heated to 80 C for 4 h, further stirring overnight at RT.

Subsequently the mixture was cooled to 5 C NaOH (4 M, 150 ml was added and the organic phase waas isolated and washed twice with Water, dried (MgSO4) and evaporated to dryness .

Yield 97 % of 7-(4-methoxycyclohexyl)-4,5-dihydro-thieno[2,3-c]pyridine , isolated as an oil.

7-(4-Methoxycyclohexyl)-4,5-dihydro-thieno[2,3-c]pyridine (2.45 g) was reduced with NaBH4 (1.11 g) in methanol (50 ml). The mixture was stirred at RT for 2 h and subsequently evaporated and extracted between dichloromethane (100 ml) and water (100 ml). The organic phase was evaporated and the resulting oil was purified on silicagel using dichloromethane /methanol (9/1) as eluent.

Yield 60 % of 7-(4-methoxycyclohexyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine .The structure was confirmed by NMR and MS: M+ 251.

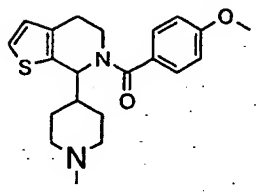
7-(4-Methoxycyclohexyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine (0.1 g) , 4-methoxybenzoyl chloride (0.081 g) , and triethylamine (0.105 ml) were reacted in toluene (5 ml) as described in example 2.

Reaction time overnight. Rinse up procedure exactly as described in example 2. Yield 0.143 g crude

[7-(4-Methoxycyclohexyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-6-yl]-(4-methoxyphenyl)-methanone, MS : M+ = 385.

EXAMPLE 5

[7-(1-Methylpiperidin-4-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-6-yl]-(4-methoxyphenyl)-methanone



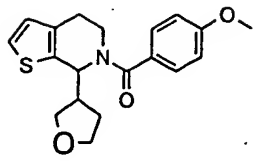
2-(3-Thienyl)ethanamine (3 g) was treated with 1-methylpiperidine-4-carboxylic acid (4.24g) , HOBT (3.18 g) , and EDAC (6.78 g) in DMF (180 ml).Procedure exactly as described in example 4. Yield 1.22 g crystals of 1-methylpiperidine-4-carboxylic acid (2-thiophen-3-yl-ethyl)-amide, identified by NMR and MS : M+ 252.

1-Methylpiperidine-4-carboxylic acid (2-thiophen-3-yl-ethyl)-amide (1.2 g) POCl3 (1.22 ml) were reacted in toluene (50 ml) exactly as described in example 4. 1.1 g of [7-(1-Methylpiperidin-4-yl)-4,5,-dihydrothieno[2,3-c]pyridine was isolated identified by NMR and MS: M+= 234.

7-(1-Methylpiperidin-4-yl)-4,5,-dihydrothieno[2,3-c]pyridine (0.1 g) , 4-methoxybenzoyl chloride (0.086 g) , and triethylamine (0.112 ml) were reacted in toluene (5 ml) exactly as described in example 4. Yield 90 % of crude [7-(1-Methylpiperidin-4-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-6-yl]-(4-methoxyphenyl)-methanone . MS: M+ = 370. .

EXAMPLE 6

[7-(4-Tetrahydrofuran-3yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-6-yl]-(4-methoxyphenyl)-methanone



2-(3-Thienyl)ethanamine (3 g) was treated with tetrahydro-3-furoic acid (2.74 g), HOBT (3.18 g), and EDAC (6.78 g) in DMF (180 ml).Procedure exactly as described in example 4. Yield 3.37 g hard oil of tetrahydro-3-furoic acid (2-thiophen-3-yl-ethyl)-amide, identified by NMR and MS : M+ 225.

Tetrahydro-3-furoic acid (2-thiophen-3-yl-ethyl)-amide(3.35 g) ,POCl3 (4.06 ml) were reacted in toluene (150 ml) exactly as described in example 4. 2.77 g of 4-tetrahydrofuran-3-yl-4,5,-dihydrothieno[2,3-c]pyridine was isolated identified by NMR and MS: M+= 207.

7-(4-Tetrahydrofuran-3-yl)-4,5,-dihydrothieno[2,3-c]pyridine(0.1 g) , 4-methoxybenzoyl chloride (0.097 g) , and triethylamine (0.126 ml) were reacted in toluene (5 ml) exactly as described in example 4. Yield 0.148 g of crude [4-tetrahydrofuran-3-yl-4,5,-dihydrothieno[2,3-c]pyridine]-(4-methoxyphenyl)-methanone . MS: M+ =343 .

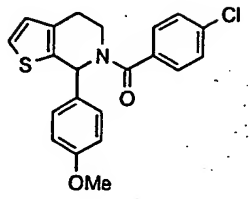
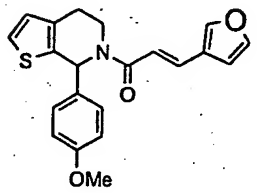
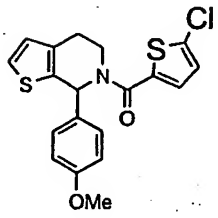
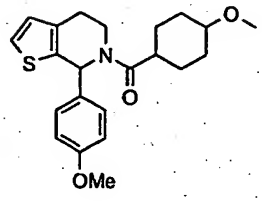
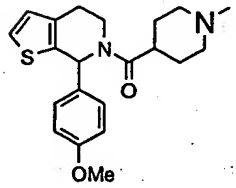
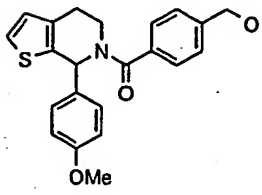
EXAMPLE 7- 41

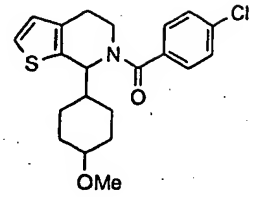
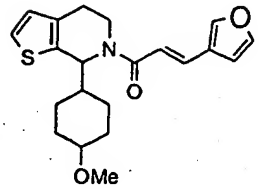
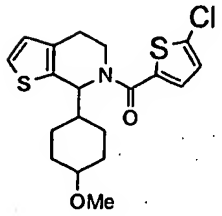
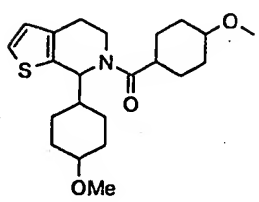
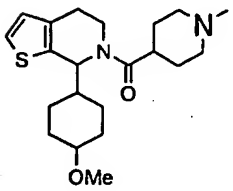
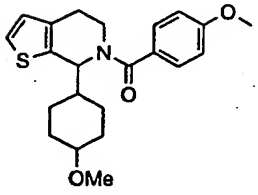
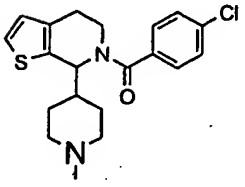
The following compounds were made according to the reaction scheme described in method c) above, using the following reaction conditions:

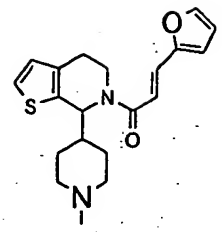
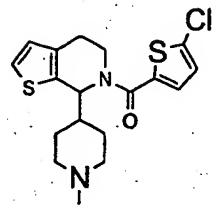
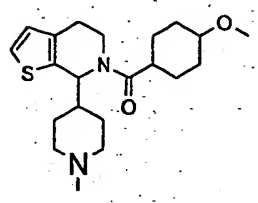
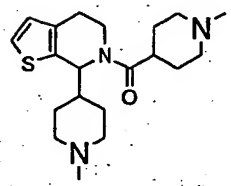
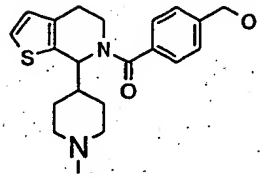
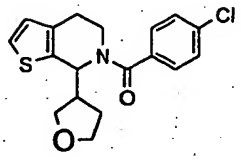
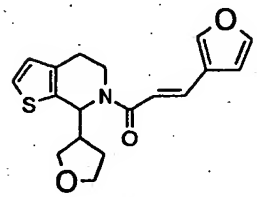
The carboxylic acid (0.15 mmol) , HOBt (0.15 mmol) , EDAC (0.15 mmol) and 7-substituted 4,5,6,7-tetrahydrothieno [2,3-c] pyridine. (0.15 mmol) were mixed in DMF (1 ml) and stirred at RT overnight.

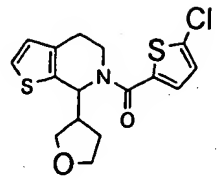
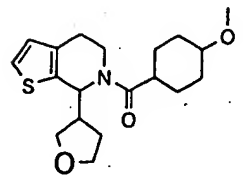
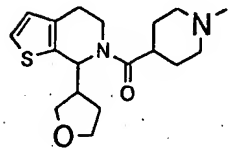
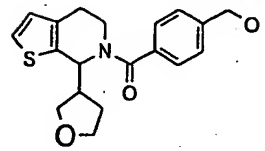
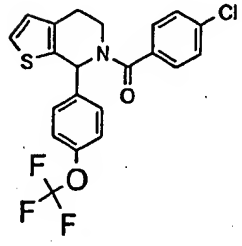
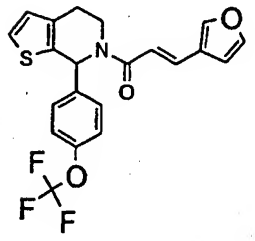
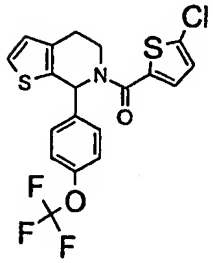
Ethyl acetate (1.5 ml) and saturated saline (1 ml) were added , the organic phase was separated and evaporated to dryness.

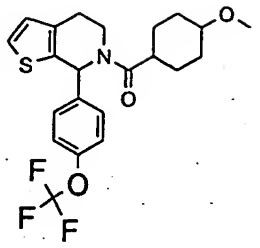
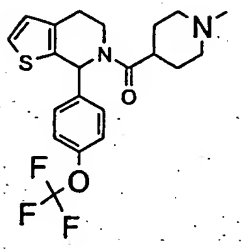
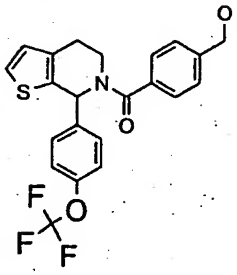
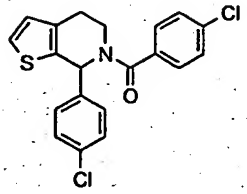
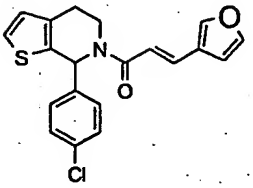
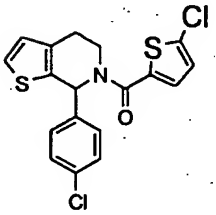
The identity of the product was confirmed by HPLC /MS.

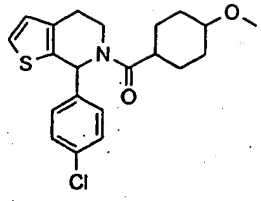
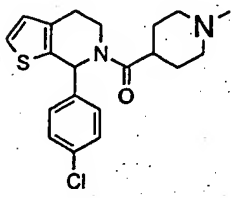
Example	Structure	HPLC/MS Rt (min)	m/z (M+1)
7		15.55	384
8		14.17	366
9		16.02	390
10		13.80 (60%) 13.35 (40%)	386
11		8.48	371
12		11.90	380

13		14.70 (60%) 15.25 (38%)	390
14		13.17 (46%) 13.82 (45 %)	372
15		15.32 (61%) 15.77 (39%)	396
16		12.89 (26%) 12.87 (25 %) 12.28 (22 %) 13.58 (20 %)	392
17		8.20 (14.5%) 8.53 (11%)	377
18		10.73 (62%) 11.57 (34 %)	386
19		8.73	375

20		8.23	357
21		8.67	381
22		7.95 (61 %) 7.60 (38%)	377
23		5.68	362
24		7.14	371
25		13.12	348
26		11.57	330

27		13.63	354
28		10.12 (54 %) 10.62 (31 %)	350
29		6.92	335
30		9.17 (58%) 9.35 (37%)	344
31		17.22	438
32		16.05	420
33		17.63	444

34		16.02 (60 %) 15.73 (39%)	440
35		9.88	425
36		14.38	434
37		16.75	389
38		15.48	370
39		17.25	395

40		15.40 (60%) 15.08 (37%)	390
41		9.43	376

Example 42-65

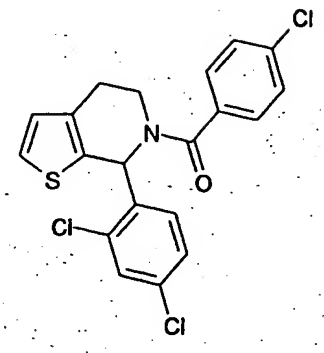
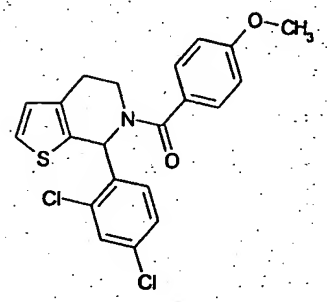
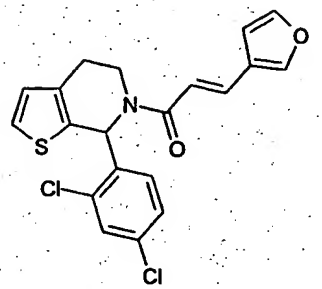
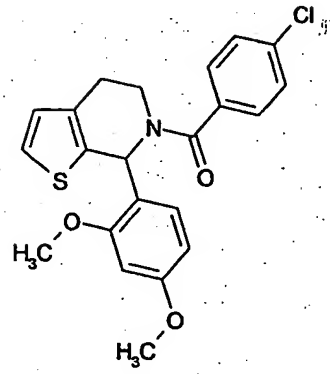
The following compounds were made according to the reaction scheme described in method c) above, using the following reaction conditions:

7-substituted 4,5,6,7-tetrahydrothieno [2,3-c] pyridine. (125 mg, 1 eqv) , the carboxylic acid (1.1eqv) , HOBt (1.5eqv) , and EDAC (1.0 eqv) were mixed in DMF (1 ml) and stirred at RT overnight.

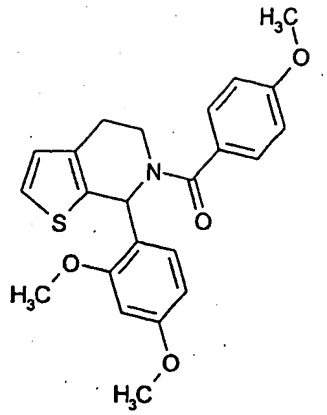
Dichloromethane (4 ml) was added and the mixture extracted with the following series of solvents: a) NaOH (1M,4 ml); b) H2O (4 ml); c) HCl (1M,4ml); d) H2O (4 ml) and e) brine (4ml).

The resulting organic phase was separated and evaporated to dryness.

The identity of the product was confirmed by HPLC /MS.

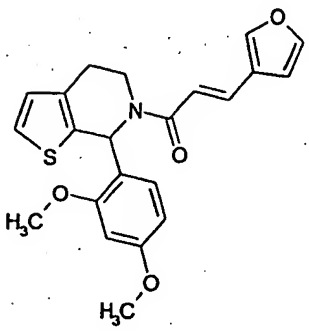
Example	STRUCTURE	HPLC/MS ,m/z (M+1)
42		m/z: 421 RT: 7,12 ELS: 65%
43		m/z: 417 RT: 6,71 ELS: 50%
44		m/z: 404 RT: 6,58 ELS: 98%
45		m/z: 413 RT: 6,29 ELS: 70%

46



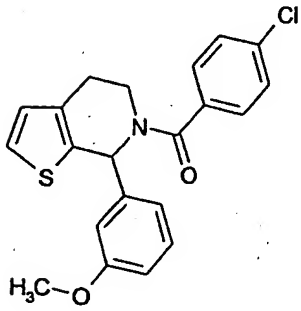
m/z: 409 RT: 5,82 ELS: 77%

47



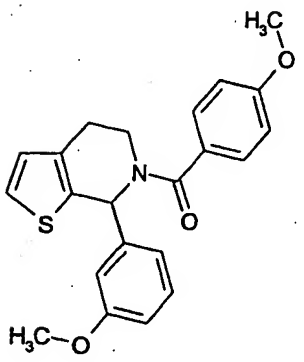
m/z: 395 RT: 5,78 ELS: 98%

48



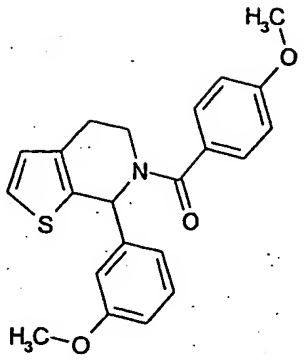
m/z: 384 RT: 6,39 ELS: 100%

49



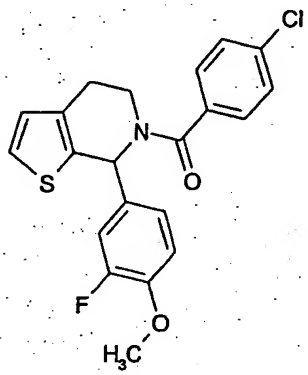
m/z: 380 RT: 5,39 ELS: 73%

50



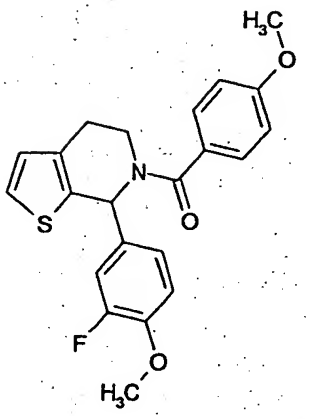
m/z: 365 RT: 5,85 ELS: 100%

51



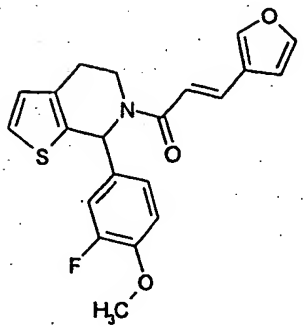
m/z: 401 RT: 6,40 ELS: 401

52



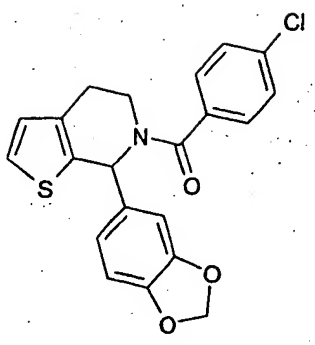
m/z: 397 RT: 5,97 ELS: 64%

53



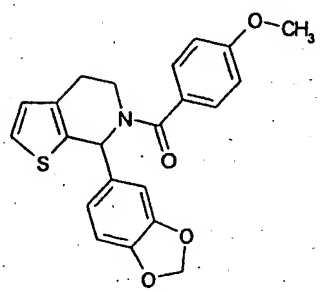
m/z: 383 RT: 5,87 ELS: 100%

54



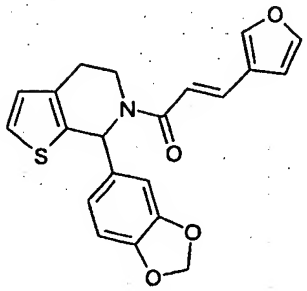
m/z: 397 RT: 6,30 ELS: 97%

55



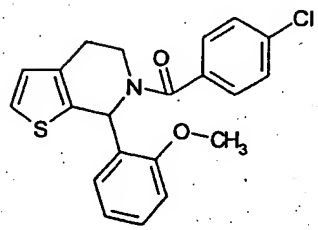
m/z: 394 RT: 5,87 ELS: 73%

56



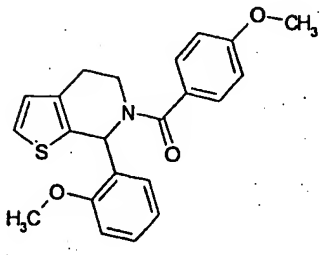
m/z: 379 RT: 5,77 ELS: 100%

57

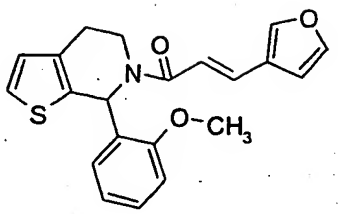


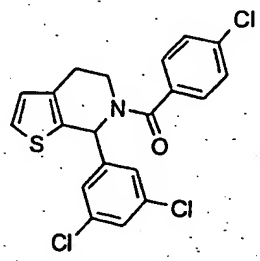
m/z: 384 RT: 6,37 ELS: 100%

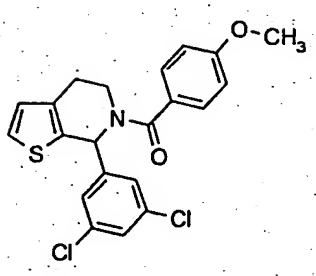
58

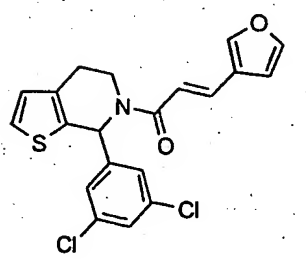


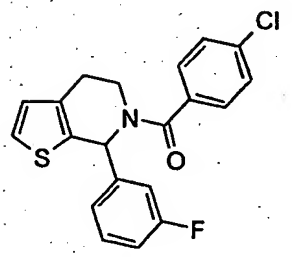
m/z: 380 RT: 5,38 ELS: 75%

59  m/z: 366 RT: 5,84 ELS: 100%

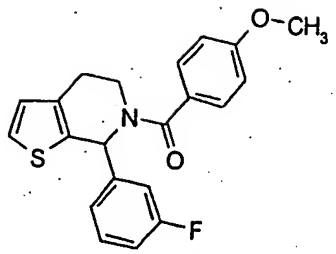
60  m/z: 422 RT: 7,36 ELS: 95%

61  m/z: 418 RT: 6,97 ELS: 80%

62  m/z: 404 RT: 6,88 ELS: 100%

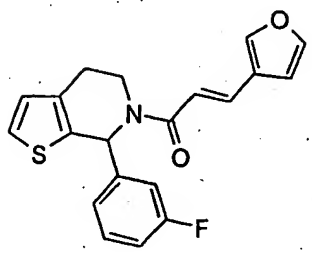
63  m/z: 372 RT: 6,52 ELS: 100%

64



m/z: 368 RT: 5,38 ELS: 67%

65

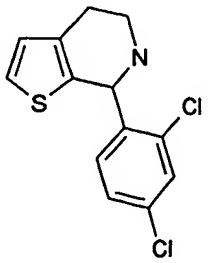


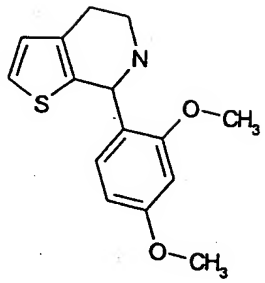
m/z: 354 RT: 6,00 ELS: 100%

Example 66.

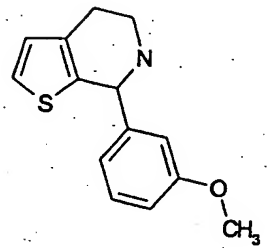
7-substituted 4,5,6,7-tetrahydrothieno [2,3-c] pyridine intermediates.

The 7-substituted 4,5,6,7-tetrahydrothieno [2,3-c] pyridine intermediates were prepared as described in example 2 from equimolar amounts of appropriate substituted benzaldehyde (0.0078 mol) and 2-(3-thienyl)ethaneamine (0.0078 mol) in dry ethanol (8 ml) by shaking for 3 days at room temperature . The mixture was subsequently evaporated to dryness and the resulting oil treated with trifluoroacetic acid (20 ml) by stirring for 24h followed by addition af NaOH (2M, 10 ml). Extraction with dichloromethane (10 ml) followed by evaporation gave the required starting 7-substituted 4,5,6,7-tetrahydrothieno [2,3-c] pyridines .
Identity and yield estimated from the HPLC/MS spectra.

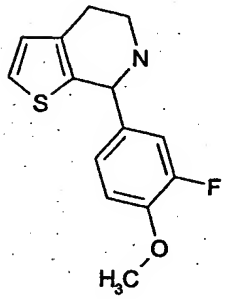
STRUCTURE	LC-MS (electrospray)
	m/z: 284 RT: 4,47 ELS: 91%



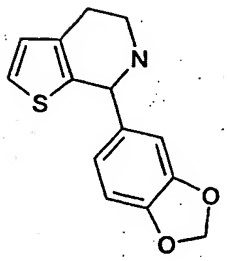
m/z: 276 RT: 4,20 ELS: 95%



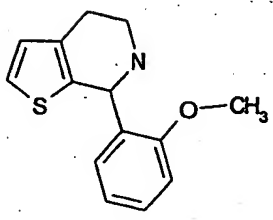
m/z: 246 RT: 4,12 ELS: 100%



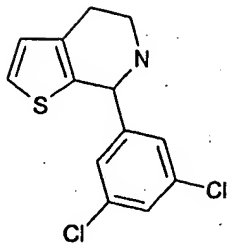
m/z: 264 RT: 4,17 ELS: 97%



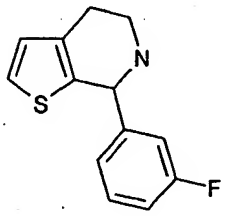
m/z: 260 RT: 4,05 ELS: 100%



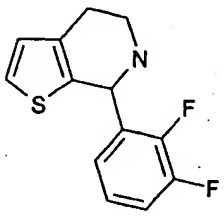
m/z: 246 RT: 4,15 ELS: 100%



m/z: 284 RT: 4,62 ELS: 94%



m/z: 233 RT: 4,08 ELS: 100%



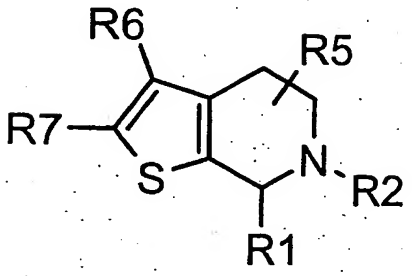
m/z: 252 RT: 3,97 ELS: 90%

General:

The HPLC-MS analyses were performed on a PE Sciex API 100 LC/MS System using a WatersTM 3 mm x 150 mm 3.5 µ C-18 Symmetry column and positive ionspray with a flow rate at 20 µL/minute. The column was eluted with a linear gradient of 5-90% A, 85-0% B and 10% C in 15 minutes at a flow rate of 1 ml/min (solvent A = acetonitrile, solvent B = water and solvent C = 0.1% trifluoroacetic acid in water).

CLAIMS

1. A compound of the general formula I



Formula (I)

wherein

R1 is a saturated straight or branched C_{1-8}-hydrocarbon chain optionally substituted with one or more substituents,

an unsaturated straight or branched C_{2-8}-hydrocarbon chain optionally substituted with one or more substituents,

a saturated C_{3-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,

an unsaturated C_{5-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,

Q optionally substituted with one or more substituents or

aryl optionally substituted with one or more substituents.

R2 is a saturated straight or branched C_{1-8}-hydrocarbon chain optionally substituted with one or more substituents,

an unsaturated straight or branched C_{2-8}-hydrocarbon chain optionally substituted with one or more substituents,

a saturated C_{3-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,

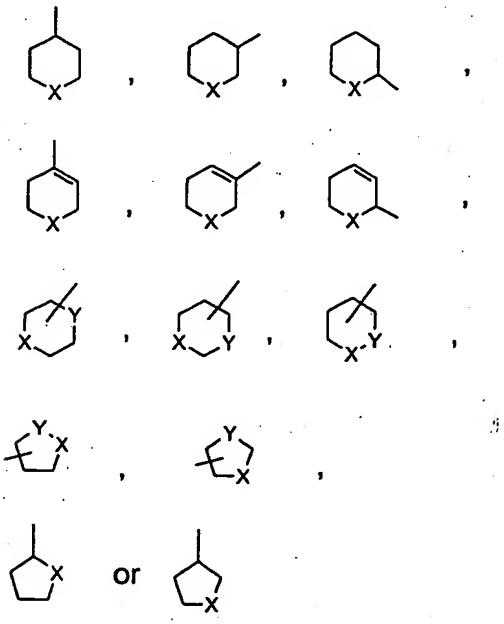
an unsaturated C_{5-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,

aralkyl optionally substituted with one or more substituents or

COR3 optionally substituted with one or more substituents,

R3 is a saturated straight or branched C_{1-8}-hydrocarbon chain optionally substituted with one or more substituents,
an unsaturated straight or branched C_{2-8}-hydrocarbon chain optionally substituted with one or more substituents,
a saturated C_{3-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,
an unsaturated C_{5-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,
an aryl optionally substituted with one or more substituents,
an aralkyl optionally substituted with one or more substituents or
W optionally substituted with one or more substituents.

Q and W are independently selected from the list consisting of



X and Y are independently selected from the group consisting of NR4, O, S, >SO, $>SO_2$,

and **R4** is selected from the list consisting of hydrogen,
a saturated straight or branched C_{1-8}-hydrocarbon chain optionally substituted with one or more substituents,

an unsaturated straight or branched C_{2-8}-hydrocarbon chain optionally substituted optionally substituted with one or more substituents,

a saturated C_{3-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,

an unsaturated C_{5-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents,

C_{1-8}-acyl, C_{1-8}-alkoxycarbonyl, or mono- or dialkylcarbamoyl,

R5, R6, R7 being independently selected from amino-C_{1-6}-alkyl, hydroxy-C_{1-6}-alkyl, hydrogen, C_{1-6}-alkyl, aryl, aralkyl, aryloxy, aryloxy-C_{1-6}-alkyl, benzyl, halogen, hydroxy, mercapto, cyano, nitro, carboxy, carbamoyl, $CONHC_{1-4}$-alkyl, $CON(C_{1-4}alkyl)_2$, C_{1-4}-acyl, C_{1-4}-alkoxy , C_{1-4}-alkylthio, $-SOC_{1-6}$-alkyl, $-SO_2C_{1-6}$-alkyl, C_{1-4}-alkoxycarbonyl, C_{1-4}-alkanoyloxy, amino, optionally substituted mono- or di-C_{1-6}-alkylamino, acylamino, $-NC_{1-4}$-alkylCOC_{1-4}-alkyl, -SO3H, -SO2NH-C_{1-6}-alkyl, tetrazolyl, perhalomethyl , perhalomethoxy

each of the above substituents being selected from the group consisting of halogen, hydroxyl, carboxy, carboxyalkenyl, 2-carboxyethenyl, cyano, nitro, carbamoyl, C_{1-8}-alkylcarbamoyl (preferably metanoyl), C_{1-8}-acyl (preferably acetyl, propionyl, isopropionyl), acetamido, C_{1-8}-alkoxy (preferably methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert.butoxy), C_{1-8}-alkyl, C_{1-8}-alkoxycarbonyl (preferably methoxycarbonyl, ethoxycarbonyl, and propoxycarbonyl), C_{1-8}-alkanoyloxy (preferably acetyloxy, propionyloxy, isopropionyloxy), C_{1-4}-alkylthio (preferably methylthio, ethylthio, propylthio, and isopropylthio), C_{1-4}-alkylsulphinyl (preferably methylsulphinyl and ethylsulphinyl), C_{1-4}-alkylsulphonyl (preferably methylsulphonyl and ethylsulphonyl), C_{1-8}-alkylamino (preferably methylamino, ethylamino), C_{1-8}-dialkylamino (preferably dimethylamino, diethylamino) C_{2-6}-cycloamines (preferably 1-piperidinyl, 1-azeridinyl, 1-pyrrolidinyl, 4-morpholinyl, 1-piperazinyl, 1-azetidinyl), aminoalkyl (preferably one having an amino containing group connected to a C_{1-8}-alkyl group as defined above, such as 2-dimethylaminoethyl and 1-pyrrolidinylmethyl), aminoalkoxy (preferably one having an amino containing group connected via a C_{1-8}-alkyl group as defined above to an oxygen atom, such as 2-dimethylaminoethoxy, 2-(4-morpholinyl)ethoxy and 1-pyrrolidinylmethoxy), aryl (preferably phenyl, furanyl and 4-pyridinyl), aryloxy (preferably phenyloxy), and aralkyloxy (e.g. benzyloxy), hydroxyalkyl, perhaloalkoxy (preferably

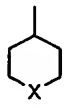
trifluroromethoxy), alkoxyaryl, C_{1-8}-acyl, perhaloalkyl (preferably trifluoromethyl), oxo, C_{1-4}-alkanoylamino-C_{1-4}-alkyl, alkoxyoxoindanyl, dimethylhydrazidyl, methylendioxy, thioxothiazolyl, imidazolyl or 2-morpholin-4-ylethoxy.

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form.

2. A compound according to claim 1, wherein R5, R6 and R7 is hydrogen.

3. A compound according to claims 1-2, wherein R2 is COR3 wherein R3 is as defined above.

4. A compound according to any of the claims 1-3 wherein R1 is Q optionally substituted with one or more substituents and Q is



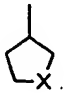
wherein X is as defined above.

5. A compound according to claim 4 wherein X is NR4 or O ,preferably NR4, wherein R4 is as defined above.

6. A compound according to claim 5 wherein R4 is a saturated straight or branched C_{1-8}-hydrocarbon chain optionally substituted with one or more substituents.

7. A compound according to claim 6 wherein R4 is methyl.

8. A compound according to any of the claims 1 -3 wherein R1 is Q optionally substituted with one or more substituent and Q is



wherein X is as defined above.

9. A compound according to claim 8 wherein X is O.

10. A compound according to any of the claims 1-3 wherein R1 is N-methylpiperidinyl, tetrahydrofuryl or tetrahydropyranyl.

11. A compound according to claim 10 wherein R1 is tetrahydropyran-4-yl, tetrahydrofuran-3- yl or 1-methylpiperidin-4-yl.

12. A compound according to any of the claims 1-3 wherein R1 is optionally substituted phenyl, thienyl preferably 2-thienyl, 3-thienyl, 4-thienyl 5-thienyl or furanyl, preferably 2-furanyl, 3-furanyl, 4-furanyl, 5-furanyl, Benzo[1,3]dioxol, preferably Benzo[1,3]dioxol-5yl, pyridyl or cyclohexyl.

13. A compound according to claim 12 wherein the substituents of R1 are selected from the group consisting of halogen, perhaloalkyl, perhaloalkoxy, C_{1-6}-alkoxy, C_{1-8}-alkyl ,C_{1-8}-alkylamino, C_{1-8} -dialkylamino or C_{2-5} -cycloalkylamino.

14. A compound according to claim 13 wherein the substituents of R1 are selected from the group consisting of chloro, fluoro, trifluoromethyl, trifluoromethoxy, methoxy, methyl or dimethylamino.

15. A compound according to any of the claims 1-3 wherein R1 is selected from the group consisting of phenyl, 4-chlorophenyl, 3-fluorophenyl, 2,4-chlorophenyl, 3,5-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 4-dimethylaminophenyl, 4-pyridyl, 2-thienyl, 5-chloro-2-thienyl, 3-chloro-2-thienyl, Benzo[1,3]dioxol-5yl, cyclohexyl or 4-methoxycyclohexyl.

16. A compound according to any of the claims 1-15 wherein R3 is a saturated straight or branched C_{1-8}-hydrocarbon chain optionally substituted with one or more substituents.

17. A compound according to claim 16 wherein R3 is a saturated straight or branched C_{1-4}-alkyl optionally substituted with one or more substituents.

18. A compound according to any of the claims 1-15 wherein R3 is an unsaturated straight or branched C_{2-8}-hydrocarbon chain optionally substituted with one or more substituents.

19. A compound according to claim 18 wherein R3 is an unsaturated straight or branched C_{2-4}-alkenyl optionally substituted with one or more substituents.

20. A compound according to any of the claims 1-15 wherein R3 is a saturated C_{3-8}-alicyclic hydrocarbon group optionally substituted with one or more substituents.

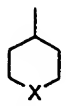
21. A compound according to claim 20 wherein R3 is a saturated cyclohexyl optionally substituted with one or more substituents.

22. A compound according to any of the claims 1-15 wherein R3 is an aryl optionally substituted with one or more substituents.

23. A compound according to claim 22 wherein R3 is phenyl, alkoxyphenyl, dialkoxyphenyl, hydroxyphenyl, indanyl, imidazolyl, pyridyl, benzofuranyl, indolyl, benzimidazolyl, thienyl, furanyl, pyranyl optionally substituted with one or more substituents.

24. A compound according to any of the claims 1-15 wherein R3 is W optionally substituted with one or more substituents wherein W is as defined above.

25. A compound according to claim 24 wherein W is optionally substituted with one or more substituents and W is



wherein X is as defined above.

26. A compound according to claim 25 wherein X is NR4 , wherein R4 is as defined above.

27. A compound according to claim 26 wherein R4 is a saturated straight or branched C_{1-8}-hydrocarbon chain optionally substituted with one or more substituents or R4 is a C_{1-8}-acyl.

28. A compound according to claim 27 wherein R4 is methyl or methanoyl.

29. A compound according to any of the claims 1-28 wherein the substituents being selected from the group consisting halogen, hydroxyl, C_{1-4}-alkoxy, C_{1-4}-alkyl, C_{1-4}-alkylthio, C_{1-4}-alkylsulphinyl, aryl, aryloxy, hydroxyalkyl, perhalomethoxy, C_{1-8}-acyl, perhalomethyl, oxo, C_{1-4}-alkanoylamino-C_{1-4}-alkyl, alkoxyoxoindanyl, dimethylhydrazidyl, methylendioxy, thioxothiazolyl, imidazol, aminoalkoxy, carboxy, carboxyalkenyl, cyano or C_{1-8}-alkanoyloxy.

30. A compound according to any of the claims 1-29 wherein the substituents being selected from the group consisting fluorine, chlorine, bromine, hydroxyl, methoxy, ethoxy, methyl, methylthio, methylsulphinyl, furanyl, thienyl, phenyl, indolyl, pyranyl, dimethoxyphenyl, methoxyphenyl, hydroxyphenyl, hydroxymethyl, trifluoromethoxy, trifluoromethyl, imidazol, methanoyl, oxo, methanoylamino-methyl, methoxyoxoindanyl, dimethylhydrazidyl, methylendioxy, thioxothiazolyl, carboxy, cyano, acetamido, nitro, acetyl, acetyloxy, dimethylamino, 2-dimethylaminoethoxy, 2-carboxyethenyl or 2-morpholin-4-ylethoxy .

31. A compound according to any of the claims 1-3 wherein R2 is COR3 wherein R3 is selected from the group consisting of phenyl, 3-methoxyphenyl, 4-methoxyphenyl 4-chlorophenyl, 4-trifluoromethylphenyl, 4-methylphenyl, 3,4-dimethoxyphenyl, 4-ethoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, 4-dimethylaminophenyl, 4-bromophenyl, 4-hydroxyphenyl, 4-hydroxymethylphenyl, 4-nitrophenyl, 4-cyanophenyl, 4-methylthiophenyl, 4-methylsulfonylphenyl, 4-acetylphenyl, 4-acetamidophenyl, 4-acetoxyphenyl, 3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3-chloro-4-methoxyphenyl, indolyl, 1H-indol-5-yl, and 1H-benzimidazol-5-yl, 2-(4-methoxyphenyl)-ethenyl, 2-(3-methoxyphenyl)-ethenyl, 2-(4-chlorophenyl)-ethenyl, 2-(4-fluorophenyl)-ethenyl, 2-(4-trifluoromethylphenyl)-ethenyl, 2-(4-methoxyphenyl)-ethyl, 2-(4-chlorophenyl)-ethyl, 4-chlorobenzyl, 4-methoxybenzyl, 2-(2-furyl)-ethenyl, 2-(4,5-dimethyl-2-furyl)-ethenyl, 2-(5-methyl-2-furyl)-ethenyl, 2-(3-furyl)-ethenyl, 2-(2-thienyl)-ethenyl, 2-(3-thienyl)-ethenyl, or 4-methoxyphenyl-2-ethenyl, 4-pyridyl, 5-hydroxypyrazin-2-yl, 5-chloro-6-hydroxypyridin-3-yl, 2-chloropyridin-3-yl, benzofuran-2-yl, benzothiophen-2-yl-, 7-methoxybenzofuran-2-yl, furyl, thienyl, chlorothienyl, 5-chlorothiophen-2-yl, or benzimidazol, 1H-benzimidazol-5-yl,

4-methoxycyclohexyl, 4-oxycyclohexyl, N-methylpiperidinyl, tetrahydrofuryl, tetrahydropyranyl, 4-(2-carboxyethenyl)phenyl, 4-(2-dimethylaminoethoxy)phenyl or 4-(2-morpholin-4-ylethoxy)phenyl.

32. A salt of a compound according to the preceding claim with a pharmaceutically acceptable acid or base.

33. A pharmaceutical composition comprising, as an active ingredient, a compound according to any one of claims 1 - 31, or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

34. The pharmaceutical composition according to claim 33 in the form of an oral dosage unit or a parenteral dosage unit.

35. A compound according to any of the claims 1 - 31 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use.

36. A compound according to any of the claims 1 - 31 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use in the treatment or prevention of diseases of the endocrinological system, preferably hyperglycaemia or diabetes.

37. A compound according to any of the claims 1 - 31 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form, characterized by having a glucose-6-phosphatase inhibitory activity corresponding to an IC_{50} value of less than 100 μM, preferably less than 10 μM, more preferably less than 1 μM, still more

preferably less than 100 nM.

38. The use of a compound according to any of the claims 1 - 31 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament.

39. The use of a compound according to any of the claims 1 - 31 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament for the treatment or prevention of diseases of the endocrinological system, preferably hyperglycaemia or diabetes.

40. The use of a compound according to any of the claims 1 - 31 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament for the treatment or prevention of glycogen storage disease or hypoglycaemia.

41. A method of treating or preventing diseases of the endocrinological system, preferably hyperglycaemia or diabetes in a subject in need thereof comprising administering an effective amount of a compound according to any one of the preceding compound claims to said subject.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00448

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 495/04, A61K 31/4365, A61P 3/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9840385 A1 (NOVO NORDISK A/S), 17 Sept 1998 (17.09.98)	1-41
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X	WO 9634870 A1 (SYNTHELABO), 7 November 1996 (07.11.96), see compound 1, page 19	1-41
	--	
X	US 4076819 A (JEAN-PIERRE MAFFRAND), 28 February 1978 (28.02.78), see example 9, deriv. 11	1,33-38
	--	
X	US 3497529 A (HANS OTT), 24 February 1970 (24.02.70), see examples 4-6	1,2,12-14, 29-30,33-38
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 December 1999	20-01-2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anna Sjölund/ELY Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00448

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5294621 A (RONALD K. RUSSELL), 15 March 1994 (15.03.94), see Table VI, 9n-cis	1,21,15, 33-38
X	STN International, File CA, CA accession 85:160017, Devani, M.B. et al: "Synthesis of 2-aminothiophenes and thieno (2,3-d)pyrimidines"; Indian J. Chem., Sect. B, 14B(5), 357-60	1,12,15, 33-38
X	US 4075340 A (JEAN-PIERRE MAFFRAND), 21 February 1978 (21.02.78), see example 3	1,2,33-38
X	WO 9215592 A1 (DR. LO. ZAMBELETTI S.P.A.), 17 Sept 1992 (17.09.92)	1-3,17,29, 33-38
X	STN International, File CA, CA accession no. 99:175627, Knabe, Joachim et al: "Dihydroisoquinoline rearrangement, XXXIV: 7-Allyl-6-methyl-6,7-dihydrothieno(2,3-c)pyridine"; Arch.Pharm. (Weinheim,Ger.), 316/10), 831-4 (German) 1983	1,12,15
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00448

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CA, CA accession no. 79:49080, Chaykovsky, M. et al: "2,4-Diamino-thieno(2,3-d)pyrimidines as antifolates and anti-malarials. 2. Synthesis of 2,4-diaminopyrido (4',3':4,5)thieno(2,3-d)pyrimidines and 2,4-diamino-8H-thiopyrano(4',3':4,5)thieno(2,3-d)pyrimidines"; J. Med. Chem., 16(3), 188-91 (English) 1973	1,12,33,38
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X	STN International, File CA, CA accssion no. 114:122254, Sukumaran, P. et al: "Synthesis of 4-(arylamino)thioxothieno(2,3-d)pyrimidines"; Indian J. Chem., Sect. B, 29B(11), 1070-3 (English) 1990	1,12,15
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK99/00448

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 41
because they relate to subject matter not required to be searched by this Authority, namely:

See extra sheet*

2. ☒ Claims Nos.: 1,33-38(all in part)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See extra sheet**

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

*Claim 41 relate to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound(s)/composition(s).

** The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many document were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Art. 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has mainly been restricted to:
The compounds prepared in the examples.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/DK 99/00448

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US 5294621 A	15/03/94	NONE	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/DK 99/00448

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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